Psychological and behavioural within-participant predictors of adherence to oral HIV Pre-Exposure Prophylaxis (PrEP)

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Executive Summary

Background

The introduction and dissemination of antiretroviral therapy (ART) has meant that HIV (Human Immnodeficiency Virus) has transitioned from being a fatal illness to chronic healthcare condition (Montaner et al, 2014). HIV has lifelong treatment implications and represents a burden for people with HIV (e.g. managing medication side effects) as well as contributing to significant healthcare costs (Laryea & Gien, 1993; Nakagawa et al, 2015).

The United Kingdom (UK), had an estimated 101,200 people living with HIV in 2015 and approximately 6,095 of these people were newly diagnosed in the same year (Public Health England (PHE), 2016; Wilson & Halperin, 2008). Despite various HIV prevention initiatives (e.g. increased HIV testing and earlier initiation of ART to reduce the infectiousness of HIV) between 2000 to 2013 HIV incidence rates remained relatively stable in the UK (Aghaizu et al, 2016; Birrell et al, 2013; Phillips et al, 2013). To the contrary, recent data has indicated that rates have steadily increased by 20% between 2007 and 2015 in those deemed most at risk in the UK; men who have sex with other men (MSM) (Phillips et al, 2013; PHE, 2017).

Newer initiatives include the introduction of oral pre-exposure prophylaxis (PrEP). PrEP involves people who are HIV-negative taking an antiretroviral drug. When taken, if HIV exposure then occurs, this antiretroviral drug stops the virus entering cells and replicating (i.e. the person remains HIV negative) (Seifert et al, 2014). Current World Health Organisation (WHO) guidelines only advocate daily-dosing regimens (i.e. one tablet taken every day) for HIV negative MSM at high-risk of HIV acquisition. Research

suggests that for PrEP to be effective MSM sexually active individuals need to take at least four doses a week regardless of sexual activity levels (Grant, 2014).

The safety and biological efficacy of PrEP to prevent HIV acquisition has been demonstrated by placebo-controlled trials within MSM and heterosexual samples (Grant et al, 2010; Grant et al, 2014; Baeten et al, 2012; Molina et al, 2015; McCormack et al, 2016a; Thigpen et al ,2012; Choopanya et al, 2013). However, when implemented PrEP has shown wide ranging effectiveness relative to placebo ranging from -49% to 86%. These wide-ranging results have been explained by varied adherence (Fonner et al, 2016). This means that PrEP implementation must be considered as bio-behavioural due to the factors (i.e. adherence) that moderate its efficacy (Kippax & Stephenson, 2012). At present, research has not concluded whether a specific theoretical model accurately explains PrEP adherence. In addition, Haberer's (2016) review highlighted that few PrEP adherence interventions have been developed and evaluated. Understanding the predictors of PrEP adherence is crucial to the development of a theoretical framework, tailored adherence interventions and to help to ensure successful PrEP implementation.

Systematic Review

The literature above highlights that adherence is critical for maximizing the effectiveness and public health impact of PrEP to prevent HIV infection. Understanding the factors associated with PrEP adherence/non-adherence is crucial to guiding the development of a theoretical framework as well as PrEP adherence interventions. Studies investigating medication adherence within different study populations (i.e HIV positive individuals), examining predictors of PrEP *uptake* or exploring hypothetical facilitators and barriers to PrEP *use*, have limited generalisability to understanding *adherence* amongst actual PrEP users. Therefore, the current systematic review synthesised the literature exploring factors related to PrEP adherence amongst MSM. Studies were included if they reported statistical relationships with, or given reasons for, PrEP adherence/non-adherence amongst MSM PrEP users at high-risk of HIV acquisition. Twenty studies (qualitative n=5, quantitative n=15) met the review's inclusion criteria. The review described and evaluated the reviewed studies, synthesised the data, and the direction of relationships were examined. Across studies, twenty factors were measured and analysed in relation to PrEP adherence. Eleven factors showed inconsistent findings across studies and three factors were only measured once. Variables examined by three or more studies where the majority reported or showed a relationship with PrEP adherence included: older age, stable housing, higher levels of HIV risk perception and actual risk behaviours, routine and planning, lifestyle factors (i.e. less travel and being less busy), less anticipated stigma if PrEP use was disclosed, not being African-American, less anticipated or actual side-effects and support from others. The review demonstrated that adherence to PrEP may be influenced by several factors at individual, interpersonal and structural levels. The review highlighted potentially

modifiable factors related to PrEP adherence which could be targeted in PrEP adherence interventions. It also highlighted factors which may vary within-individual dependent on the situation. Future research could examine modifiable situational variables (psychological and behavioural) to gain a clearer understanding of how these factors could impact adherence.

Empirical Project

The effectiveness of PrEP is variable, explained by differences in PrEP adherence. PrEP adherence is often inconsistent *within* individuals, whereas most studies only investigate adherence *between* individuals. Understanding psychological and behavioural correlates of PrEP adherence is important to develop effective adherence interventions. This study investigated within-participant behavioural and psychological differences between adherent and non-adherent PrEP episodes in men who have sex with men (MSM), informed by theory (the Information-Motivation-Behavioural Skills model). Sixty-seven HIV-negative MSM at high-risk of HIV acquisition were recruited from two London sexual health clinics. All participants had followed a daily dosing PrEP regimen for at least three months and had shown inconsistent adherence (i.e. had one day when a dose was taken and one day when a dose wasn't taken) in the previous month. Participants completed a questionnaire measuring psychological and behavioural variables for both an adherent and non-adherent episode. Paired t-tests, McNemar's chi-square tests and a conditional logistic regression (CLR) model were used to analyse associations between situational behavioural and psychological factors and adherent and non-adherent events. Lower reported information about PrEP, lower behavioural skills related to PrEP use and lower positive affect were associated with non-adherent episodes. There were no significant differences in

negative affect or PrEP motivation between episodes. A CLR model including information, behavioural skills and positive affect was significantly predictive of non-adherent episodes, although only behavioural skills was statistically significant independently. Behavioural factors including weekend days, lack of reminders, non-normality of the day, being out of the home, not being alone and substance use were also associated with PrEP non-adherence. Findings suggested that situational psychological factors are important for PrEP adherence. Theoretically, findings give support to some aspects of the IMB model to help explain PrEP adherence, however, also highlight predictors related to PrEP adherence which are not acknowledged within the model (i.e. situational behavioural factors such as location or positive affect). Adherence interventions should consider focusing on potentially modifiable situational variables (psychological and behavioural).

Integration, Impact and Dissemination

Integration

The literature within the review highlighted the problem, that is, the issue of PrEP non-adherence amongst MSM and its critical role in effective PrEP implementation to reduce HIV acquisition. This provided a clear rationale for the systematic review and empirical article which both focused on the issue of PrEP adherence within the MSM population. Specifically, both pieces aimed to examine the predictors of PrEP adherence. Opposed to previous reviews, the current review provided a summary of the key factors related to PrEP adherence amongst *actual* PrEP users which meant that review findings were more relevant to the empirical piece and could inform the factors which were explored. All studies included in the review used between-

participants' correlates of PrEP adherence (e.g. ethnicity) to make comparisons between 'good-adherers' and 'poor-adherers' which prevented the investigation of the factors related to variability in adherence across situations within an individual. This gave a clear rationale that by using a within-participant design the empirical article could expand upon the review and examine situationally-specific factors related to adherence. The review highlighted that studies had not used theory to inform the variables which they measured in relation to PrEP adherence. Therefore, it felt necessary that the empirical piece was closely linked to a theoretical model of adherence.

Impact

The World Health Organization (WHO) cites HIV as a major global public health issue. Newer preventative approaches such as PrEP have been cited as a crucial strategy to provide effective prevention and dramatically reduce HIV acquisition. A barrier to successful PrEP implementation has been non-adherence. The current review and empirical research investigated the relationship between predictors of adherence to PrEP amongst MSM who are most at risk of HIV acquisition in the UK. This research contributes knowledge regarding the factors which may be related to PrEP adherence and indicates ways in which adherence interventions could be tailored to ensure successful PrEP implementation. The potential beneficiaries of this work are a) PrEP users and their sexual partners, b) support organisations, c) clinicians administering PrEP, monitoring PrEP use or delivering PrEP adherence interventions d) policy makers/professionals involved in PrEP implementation guidelines and e) researchers (e.g. health or clinical psychologists) in the PrEP field or examining situationally-specific medication adherence on other conditions.

Dissemination

It is planned that the current research will be made more broadly available by publishing results in a journal article (i.e. AIDS & Behaviour) and submitting the empirical abstract to the 2018 HIV Research for Prevention conference. Both give the opportunity for findings to be disseminated to multiple professionals specifically within this clinical/research domain.

Service-user involvement will be crucial to establish which findings may be most of interest to the public and MSM population. I will attend LGBT/MSM specific service-user groups to gain advice about the most relevant findings as well as how and where results should be presented. Findings will be adapted for dissemination at relevant forums (i.e. LGBT and MSM specific service user groups as well as community events). This will help ensure that findings are disseminated to PrEP users, those who may not have heard of PrEP, those interested in PrEP uptake or those who have discontinued PrEP. Key findings will also be disseminated through online mediums (e.g. on recruitment sites social media platforms such as Facebook). To facilitate dissemination to clinicians it is planned that I will attend and present the key findings to team meetings and training workshops at London sexual health clinics. It is planned that I will communicate via email with drug companies, key individuals writing PrEP guidelines and to journalists. Lastly, it would be helpful to prepare a poster to present at any unanticipated opportunities that may arise.

A systematic review of the correlates of PrEP adherence in men who have sex with men (MSM)

Abstract

Pre-Exposure Prophylaxis (PrEP) is a safe and efficacious HIV prevention tool. If HIV exposure occurs, this antiretroviral drug stops the virus entering cells and replicating (i.e. the person remains HIV negative). However, when implemented, PrEP has had variable effectiveness explained by varied adherence. Understanding the factors that are related to PrEP adherence amongst actual PrEP users is important to developing effective adherence interventions and ensure successful implementation. This review investigated the factors related to PrEP adherence amongst men who have sex with men (MSM). Studies were included if they had statistically assessed relationships with, or given reasons for PrEP adherence/non-adherence amongst MSM PrEP users at high-risk of HIV acquisition. Twenty studies (qualitative n=5, quantitative n=15) met inclusion criteria. The review described and evaluated the reviewed studies, synthesised their data and the direction of relationships were examined to answer the key objectives of the review. Across studies, twenty factors were measured and analysed in relation to PrEP adherence. Eleven factors showed inconsistent findings across studies and three factors were only measured once. Variables examined by three or more studies where the majority reported or showed a relationship with PrEP adherence included: older age, stable housing, higher levels of HIV risk perception and actual risk behaviours, routine and planning, lifestyle factors (i.e. less travel and being less busy), less anticipated stigma if PrEP use was disclosed, not being African-American, less anticipated or actual side-effects and support from others. The review demonstrated that adherence to PrEP may be influenced by several factors at individual, interpersonal and structural levels. The review highlighted potentially modifiable factors related to PrEP adherence which could be targeted in PrEP adherence interventions. It also highlighted factors which may vary within-individual

dependent on the situation. Future research could examine modifiable situational variables (psychological and behavioural) to gain a clearer understanding of how these factors could impact PrEP adherence.

Introduction

HIV: General Overview

HIV (Human Immunodeficiency Virus) targets multiple cells of the immune system and replicates rapidly. Infection is associated with wide-ranging symptomology; varying from symptoms of primary infection (such as rash and fever), to serious diseases associated with a suppressed immune system (such as hepatitis) (Adler et al, 2012). The introduction and dissemination of antiretroviral therapy (ART), has changed the clinical picture of HIV; from fatal illness to chronic condition. However, these treatment initiatives require lifetime adherence to medication and represent a burden to the HIV positive individual (e.g. managing side effects) as well as having major economic implications for healthcare services (Laryea & Gien, 1993; Nakagawa et al, 2015).

Globally, 36.7 million people were estimated to be living with HIV in 2016 (UNAIDS, 2017). Levels of HIV acquisition vary notably across countries and population sub groups (UNAIDS, 2016). For example, some regions (e.g. Sub-Saharan Africa) are described as having a 'generalised' HIV epidemic (i.e. where HIV is firmly established in the general population) whereas other regions (e.g. Latin America, the Middle East, Europe, and Asia) there is a 'concentrated' HIV epidemic (i.e. where HIV has spread rapidly within specific sub-populations but is not well-established in the general population) (Wilson & Halperin, 2008).

The United Kingdom (UK) had an estimated 101,200 people living with HIV in 2015 and approximately 6,095 of these people were newly diagnosed in the same year (Public Health England (PHE), 2016). Between 2000 and 2013, there was no decrease in the incidence rates of HIV in the UK (Aghaizu et al, 2016). On the contrary, rates steadily increased by 20% between 2007 and 2015 in those deemed most at risk in the UK; gay, bisexual and men who have sex with other men (MSM) population (Phillips et al, 2013; PHE, 2017). Preventative strategies to reduce HIV transmission have included earlier initiation of antiretroviral therapy which may result in viral suppression (Vernazza et al, 2000; Wilson et al, 2009) and increased testing, which could result in HIV positive individuals changing their sexual behaviour, both reducing the risk of onward transmission (Fox et al, 2009). The lack of progress in reducing incidence rates, despite these ongoing healthcare initiatives, suggests that newer strategies must be implemented (McCormack et al., 2016a).

Pre-exposure Prophylaxis (PrEP): General Overview

One promising HIV prevention strategy is the use of oral Pre-exposure prophylaxis (PrEP). PrEP involves an antiretroviral drug and specifically those containing both tenofovir disoproxil (TDF) and emtricitabine (FTC) are currently recommended (WHO, 2016). Once optimal concentrations have been reached (i.e. up to as much as seven days of daily use), if HIV exposure occurs, this antiretroviral drug stops the virus entering cells and replicating (i.e. the person remains HIV negative) (Seifert et al, 2014).

There are two potential PrEP dosing regimens; daily or event-driven (i.e. intermittent dosing when sexually active). Evidence from iPrEX (Initiativa Profilaxis Pre-Exposicion), a multi-national randomised controlled trial (RCT), suggested that for PrEP to be effective, sexually active MSM individuals following a daily regimen need to take at least four doses a week (regardless of sexual activity levels) (Grant, 2014). For event-driven dosing to be effective, individuals must take two doses of PrEP between two and twenty-four hours before sex, a third dose twenty-four hours later and a fourth dose forty-eight hours later (Molina, 2015). The European AIDS Clinical Society and British HIV Association guidelines (McCormack et al, 2016b) recommends the consideration of both regimens, however current World Health Organisation (WHO) guidelines only advocate daily-dosing regimens. Specifically, WHO (2016) advocate that all people at substantial risk of HIV infection (i.e. populations with an HIV incidence of about 3 per 100 person-years or higher) should be offered PrEP as one part of a package of HIV prevention approaches.

Since the implementation of combined preventative strategies (i.e. increased testing and condom use, earlier initiation of ART and access to PrEP) Public Health England (2017) announced a 18% decline in HIV incidence from 2015 to 2016. This was particularly evident amongst MSM where a 21% decline was observed. This is one of the first significant shifts within this high-risk population seen in Europe. The decline was most evident in London where MSM have high testing rates and prompt access to services. PHE (2017) has attributed this progress to the combined preventative strategies and anticipates that these efforts will be reinforced further by the implementation of upcoming PrEP trials.

PrEP: Efficacy and effectiveness

PrEP has been advocated based upon placebo-controlled RCT's which have demonstrated the safety and biological efficacy of PrEP amongst MSM (Grant et al, 2010), heterosexuals (Baeten et al, 2012; Thigpen et al ,2012) and drug users (Choopanya et al, 2013). Despite promising findings, when implemented PrEP has shown wide ranging effectiveness; from -49% to 86% (Pool, Youssef, & Fisher, 2015). This common dilemma can be described as an 'efficacy-effectiveness' gap that is, when the biological efficacy of an intervention/product under optimal conditions differs when conducted in 'real-life' conditions (Masse et al, 2009).

Studies using MSM samples; iPrEx a placebo controlled randomised control trial (RCT) of TDF/FTC (TDF=tenofovir, FTC=emtricitabine) found PrEP had 44% efficacy (Grant et al, 2010) and in the open-label extension (OLE) this increased to 49% efficacy (Grant et al, 2014). The iPrEx study used a large multi-national sample (Brazil, Ecuador, Peru, South Africa, Thailand and the United States (US)). IPERGAY, a randomised trial (placebo vs TDF/FTC) using French and Canadian participants, found that PrEP had 86% efficacy (Molina et al., 2015). Similarly, the open-label PROUD RCT (TDF/FTC versus delayed waitlist) found that PrEP reduced the risk of HIV acquisition by 86% using a UK sample (McCormack et al, 2016a).

When using female participants in Africa, Fem-PrEP (comparing placebo versus PrEP in Kenya and South Africa) and VOICE (oral arm comparing TDF versus TDF/FTC versus placebo in South Africa, Uganda, and Zimbabwe) blinded trials found PrEP was ineffective as a HIV prevention strategy (Corneli et al, 2014, VanDamme et al, 2012; Marrazzo et al, 2015). Other studies conducted amongst serodiscordant couples in Africa found between 67% and 96% levels of PrEP effectiveness; the blinded Partners

PrEP study (comparing TDF versus TDF/FTC versus placebo) found PrEP was 67% (TDF) and 75% (FTC/TDF) effective at reducing the risk of HIV transmission (Baeten et al, 2012) whilst the open-label Partners demonstration project (involving TDF/FTC and antiretroviral therapy) found PrEP was 96% effective at reducing HIV incidence in Kenya and Uganda (Baeten et al, 2016). Lastly, Thigpen et al's (2012) double-blinded study (comparing TDF/FTC to placebo) found PrEP was 62% effective amongst heterosexual men and women in Botswana.

Of note, the studies described above combined PrEP within a larger package of HIV prevention strategies and all apart from IPERGAY (who followed an event-driven dosing regimen) investigated the effectiveness of daily PrEP regimens (Pool, Youssef, & Fisher, 2015).

PrEP: Prevention Cascade

The literature above highlights that the efficacy shown in clinical trials can only be achieved if an intervention is delivered, taken up by the population and adhered to (Hargreaves et al, 2016). Therefore, research must investigate the demand for, supply of and adherence to HIV prevention strategies to ensure it has a population-level impact. Specifically, the development of a prevention cascade allows multi-disciplinary evidence and interventions to be organised around each stage of implementation (Krishnaratne, Hensen, Cordes, Enstone & Hargreaves, 2016).

The implementation of PrEP can be conceptualised as a cascade which highlights the proportion of high-risk HIV negative individuals lost at each stage of implementation. Each stage in the prevention cascade represents a reduction in the effect of PrEP due

to lack of availability, unwillingness to use PrEP and non-adherence (Garnett et al, 2016). Specifically, these intervention-centric stages include:

i) all individuals who are at high risk of HIV
ii) those who have PrEP available to them/are supplied PrEP,
iii) high-risk individuals who take up PrEP,
iv) high-risk individuals who do or do not adhere to PrEP and
v) those who adhere to PrEP (and PrEP is efficacious).

Prep: Adherence

The varied results of effectiveness do not undermine the biological efficacy of PrEP but have been explained by the latter part of the prevention cascade; varied adherence (Van der Straten et al, 2012). Using meta-regression techniques, Fonner et al (2016) found that adherence was a significant moderator of PrEP effectiveness; when grouped, studies where less than 40% sample adhered well showed no preventative benefit whereas studies of adherence levels of eighty percent or more showed PrEP to be the most effective.

Examining adherence specifically amongst MSM samples, iPrEX found a 51% adherence rate (as defined by plasma concentration levels) (Grant et al, 2010) whilst iPrEX OLE found a 71% adherence rate (i.e. 51% and 71% of all people who received PrEP and had blood plasma tested had a detectable level of PrEP) (Grant et al, 2014). IPERGAY, found 43% of participants had not taken PrEP as prescribed (Molina et al, 2015). Similarly, PROUD showed 40% of MSM participants did not take medication 100% of the time and 36% intentionally did not adhere for a period (McCormack et al,

2016a). High rates of adherence were found by Project PrEPARE, a pilot RCT which found 84% of US participants had drug levels consistent with daily use (Mayer et al, 2014). Similarly, the Demo Project, a US demonstration project (i.e. adherence in 'real-life' clinic settings) found that 73%-92% of MSM participants at different timepoints had drug levels that indicated four or more doses a week were taken (Cohen et al, 2014). However, Project PrEPare, a separate US demonstration study, found only 34% of young MSM participants had drug levels needed for PrEP effectiveness (Hosek et al., 2017).

Theoretical and Clinical implications

At present, research has not concluded whether a specific theoretical model accurately explains PrEP adherence. In addition, Haberer's (2016) review highlighted that few PrEP adherence interventions have been developed and evaluated. Overall, the four interventions identified highlighted that general and enhanced counselling (the latter for those who find adherence difficult) as well as technological methods (e.g. two-way texts) can effectively support PrEP adherence (Amico et al, 2012; Liu, Stojanovski, Lester, Amico, McMahan, & Goicochea, 2014; Mayer et al, 2014; Psaros et al, 2014). All counselling interventions included addressing the facilitators and barriers to PrEP adherence. The development of these PrEP adherence interventions were informed by ART adherence interventions used for the HIV positive population. Despite this research providing a useful framework, factors associated with ART adherence may not be applicable to or capture all the relevant factors for PrEP adherence, given that predictors may differ between symptomatic (HIV positive) and asymptomatic (HIV negative) individuals (Marcus et al, 2014). Therefore, predictors of adherence must be explicitly explored within PrEP population. This could highlight

potentially modifiable factors which could be targeted within tailored PrEP adherence interventions as well as identify those most 'at-risk' of non-adherence. Understanding and synthesising the predictors of PrEP adherence could also help theoretical development to understand PrEP adherence.

Current state of knowledge re: predictors of PrEP use

There do not appear to be any reviews which have examined the predictors of PrEP adherence amongst MSM PrEP users. Systematic reviews have focused earlier in the prevention cascade, exploring factors associated with the willingness/acceptability and uptake of PrEP. Peng, Su, Fairley, Chu, Jiang, Zhuang, & Zhang, (2017) found that demographic factors (i.e. younger age, more educated and higher wealth) and cognitive factors (i.e. prior knowledge of PrEP) amongst MSM were predictive of higher acceptance of PrEP. Other cognitive factors (i.e. low self-efficacy, specifically perceived inability to achieve good adherence, beliefs that doubt the efficacy of PrEP and concerns about side effects), structural factors (i.e. affordability) and social factors (i.e. societal stigma) were barriers. Similarly, another review by Koechlin et al (2017) found that across risk groups (women, female sex workers, serodiscordant couples, transgender women [TGW], young and adolescent women, people who inject drugs and healthcare providers) greater knowledge about PrEP was associated with more willingness to use PrEP. This review also examined the barriers and facilitators to PrEP uptake. Across all risk groups they identified that cognitive factors (i.e. the perception that drugs are for people who are ill, concerns about safety and potential interactive effects with other substances such as alcohol or drugs), social factors (i,e. HIV and ART stigma), behavioural factors (i.e. low HIV risk perception), structural factors (i.e. cost) and demographic factors (lower educational level) were barriers to

PrEP use. However, social factors such as peer support and behavioural factors such as disclosure of PrEP use to peers and pill discreteness facilitated PrEP use.

One limitation of these reviews was that most studies included evaluated barriers and facilitators of hypothetical PrEP use or uptake. The factors which have been reported to facilitate or hinder PrEP use may not be generalisable to the actual PrEP taking population and predictors of adherence. The current review aims to overcome this limitation by examining correlates of adherence only in studies where PrEP was made available for actual use. This includes randomised control trials (RCT) where participants been a part of a placebo or an active arm which took PrEP medication.

Predictors of ART adherence

Antiretroviral therapy (ART) treatment for HIV positive individuals involves a combination of three drugs (referred to as highly active antiretroviral therapy or 'HAART') taken every day. ART has shown to have highly efficacy supressing HIV replication which has allowed HIV positive individuals to improve quality of life as well as lower mortality and morbidity rates (Montaner et al, 2014). However, ART requires near-perfect adherence, with this being a crucial moderating factor of HIV viral suppression and health outcomes (Adefolalu & Nkosi, 2013; Bangsberg et al, 2001; Katz et al, 2013). However, approximately 40% of people with HIV do not sufficiently adhere to their medication regimen (Spaan, van Luenen, Garnefski & Kraaij, 2018).

Research has shown a range of factors which impacts ART adherence amongst HIV positive individuals. For example, reviews and meta-analyses have identified the following adherence barriers: affective factors such as mental health difficulties including depression (Gonzalez et al, 2011, Nakimuli-Mpungu et al, 2012; Uthman et

al 2014) and substance misuse (Mills et al, 2006; Hendershot, Stoner, Pantalone, & Simoni, 2009): behavioural factors such as a change to daily routine, being away from home (Shubber et al, 2016) or experience of side effects (Al-Dakkak eet al, 2013): social factors such as increased stigma (i.e. HIV stigma) (Langebeek et al, 2014) as well as lack of social support (Ammassari et al, 2002): demographic factors such as lower socioeconomic status (Vreeman, Wiehe, Pearce, & Nyandiko, 2008): and cognitive factors such as lack of ART information (Posse et al, 2006). This research (which highlighted predictors of ART adherence in HIV positive individuals) has been used to develop effective interventions to support adherence in this population. As described above, although this research may not be generalisable to the PrEP-taking population (e.g. motivations, side effects and support may differ) it highlights that a range of behavioural, social, cognitive and affective factors can affect ART adherence which may be relevant when considering predictors of PrEP adherence/non-adherence (Haberer, 2016).

Aims and Objectives of the current review

The literature has highlighted that adherence is critical for maximizing the effectiveness and public health impact of PrEP to prevent HIV infection. Understanding the factors associated with PrEP adherence/non-adherence is crucial to guiding the development of a theoretical framework as well as PrEP adherence interventions. Studies investigating adherence within different study populations (i.e HIV positive individuals), at earlier points of the prevention cascade (e.g. predictors of uptake) or those examining exploring hypothetical facilitators and barriers to PrEP use, have limited generalisability to understanding adherence amongst actual PrEP users. Therefore, the current systematic review will synthesise the literature exploring factors that are related to PrEP adherence/non-adherence in MSM. The following research question was generated for the review:

i) Which demographic, social, behavioural, cognitive and affective factors are related to PrEP adherence/non-adherence?

Method

Eligibility criteria

Participants

All studies including HIV negative MSM (including TGW who have sex with men), aged 16 years or older and identified as being at high risk of HIV acquisition were included. Studies including other samples as well as MSM were included if MSM participants were a part of a specific sub-group analysis. All participants must have taken PrEP medication or been a part of a placebo arm in a randomised control trial (RCT) where the active arm took PrEP medication. Studies which only focused on willingness to take PrEP medication were excluded.

Independent variable

This review considered any variables statistically analysed in relation to, or given as reason for, PrEP adherence/non-adherence. These may be more specifically defined as demographic, behavioural or psychological including; social, cognitive and affective variables.

Outcome variable

The main outcome variable was PrEP adherence. All types of measurement for adherence were included in the review (e.g. self-report and blood plasma concentrations). Furthermore, all definitions of adherence/non-adherence were included (e.g. any missed dose of PrEP or four or more doses missed in one week may have been defined as ‘non-adherence’).

Types of Studies

Primary empirical research studies, and all studies regardless of design (i.e. quantitative or qualitative methodologies; cross-sectional, longitudinal and intervention; within and between participant designs) were included. No date limitations or location restrictions were made. Articles were not required to be published in peer review journals. Only studies written in English were considered for review and no grey literature search took place.

Sources of Information

Studies were identified by searching electronic databases, PubMed and PsycINFO. Searches were completed on 2nd October 2017.

Search Strategy

The key words within the search strategy used for all databases was:

- HIV preexposure prophylaxis OR PrEP OR oral PrEP AND
- uptake OR motivations OR barriers OR uptake and use OR adherence AND
- HIV OR HIV prevention OR HIV negative AND
- MSM OR men OR men who have sex with men OR gay men.

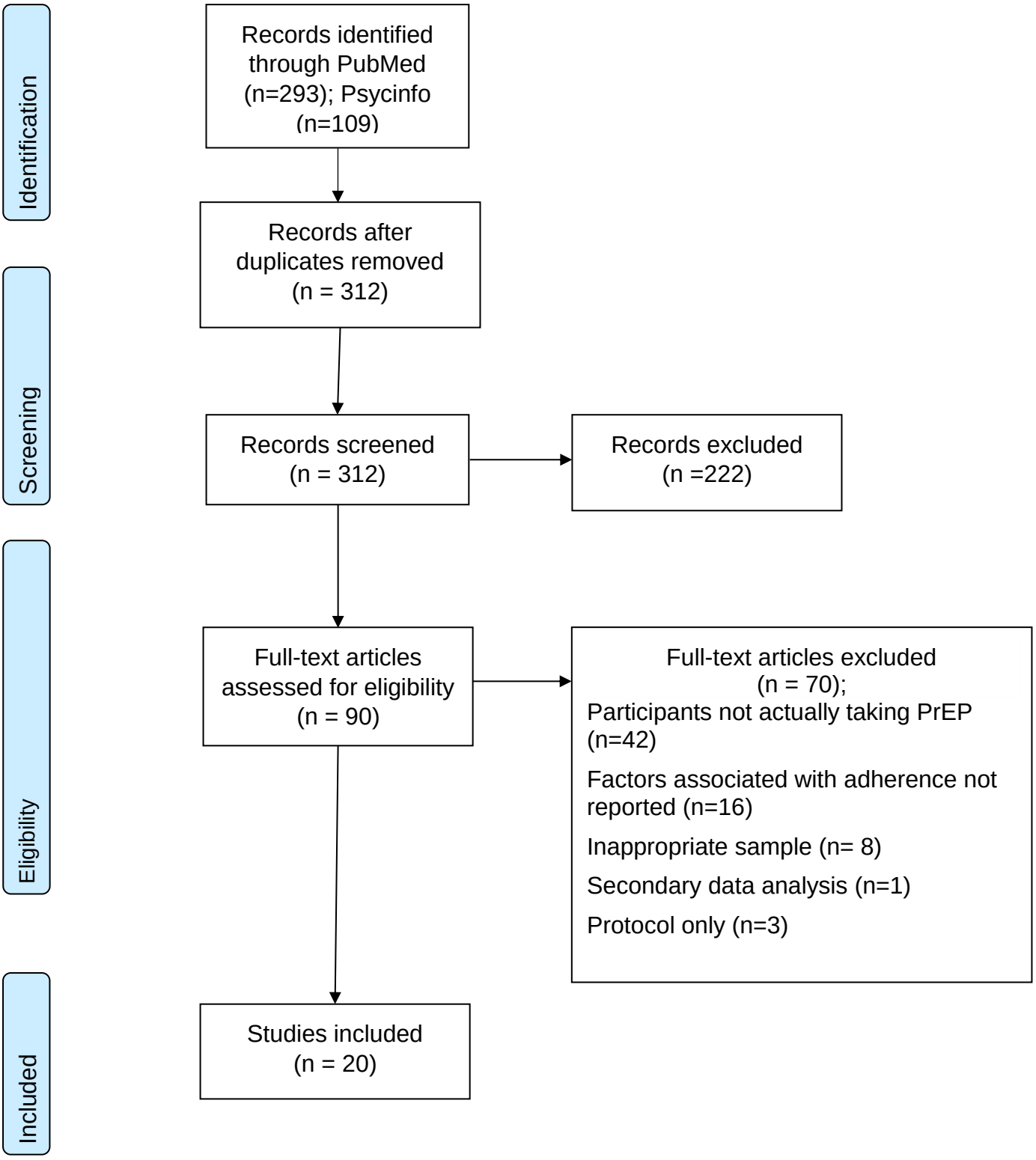
HIV pre-exposure prophylaxis / PrEP or oral PrEP were searched for as keywords in the title, with the other terms being searched for as keywords in the abstract or title.

Data collection

The data collection process followed the practice guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) (see Figure 1).

- The author carried out the search for the identification of studies, using the pre-specified search criteria outlined above.
- All duplications between databases were removed.
- Titles and abstracts were independently screened for eligibility by two reviewers (the author and an undergraduate psychology student).
- Articles considered relevant by either reviewer were retrieved in full text.
- Both reviewers independently assessed the eligibility of the retrieved articles.
- Exclusions were recorded in an Excel spreadsheet, with reasons given.
- Any disagreements were resolved by a third reviewer (the internal supervisor) to result in a final group of studies for analysis.

Figure 1: **Study Search Process**



Data Abstraction

For each included study the following details were extracted:

(a) Study information:

Authors, year of publication, location, study design and sample characteristics (including sample size, gender identity (MSM/TGW), age, ethnicity, dosing regimen, sampling strategy and response rate).

(b) Assessment tools:

Instruments used to measure adherence.

(c) Analysis:

Multivariate analyses conducted (yes/no) and study attrition rate.

Quality Assessment

A bespoke assessment tool was used to ascertain the risk of bias for included studies, based upon the Mixed Methods Assessment quality assessment tool (Pluye et al, 2011). For quantitative studies, the methodological elements assessed included two dimensions of external validity (sample representativeness and response rate) and three dimensions of internal validity (detection bias, attrition bias and confounding) (see Table 1). For qualitative studies, the methodological elements assessed included three dimensions; credibility, transferability and confirmability (see Table 2). Both reviewers (the author and undergraduate student) independently conducted the quality assessment, with a third reviewer (internal supervisor) resolving disagreements in ratings. The biases highlighted were considered in the subsequent interpretation of the data.

Table 1: ***Quality Assessment tool for quantitative studies***

External validity	
Sampling	
Representativeness of the sample for the target population	• Was the sample a consecutive or random sample, or were all the population eligible?
The percentage of selected individuals who agreed to participate	• Were at least 80% of those eligible to participate recruited?
Internal validity	
Detection bias	
Measurement of data collection methods	• Were measures of adherence objective or shown/reported to have established reliability and validity?
Attrition bias	
Number of withdrawals	• Were withdrawals reported in terms of numbers?
Percentage of participants included in final analysis	• Were at least 80% of those invited to participate in the study included in final analysis (for intervention/cohort studies)? Or was loss to follow-up after baseline 20% or less?
Control of confounding variables	
Extent to which possible confounding variables were measured	• Were important differences between groups prior to the intervention measured/identified? Or were variables that vary across the sample that might influence the outcome (e.g. age, ethnicity, regimen) measured?
Extent to which possible confounding variables were analysed	• Were possible confounding variables appropriately considered in the design (e.g. stratification, matching) or analysis (i.e., was multivariate analysis conducted)?

Table 2: ***Quality Assessment tool for qualitative studies***

Credibility	
Was the process for analysing qualitative data relevant to address the research question?	• Was (a) the method of data collection clear (e.g. in-depth interviews); (b) the form of the data clear (e.g. tape recording) and; (c) were changes explained when methods were altered during the study.
Did the representativeness of the data fit with the view of the participants?	• For example, did the study give verbatim quotes, independent analysis of the data by more than one person, peer debriefing, outside auditors, sufficient data to support the findings or consideration of data saturation
Transferability	
Were the findings transferable to other settings?	• Was at least 2 of the following used: rich detail of study participants including contextual information and demographics, sampling strategy that shows that convenience sampling was not used, ≥80% response rate,
Confirmability	
Was the analysis grounded in the data? Was appropriate consideration given to how the findings relate to researchers' influence?	• Was at least 2 of the following used: assessing the effects of the researcher during the research process, reflexivity (i.e. information about the researcher's background, education, school of thought, assumptions about the topic of interest and how the research process is influenced by this) or has the researcher explained their reaction to critical events during the study.

Data synthesis/Analysis

Inter-rater reliability for study eligibility was assessed using Cohen's Kappa. There was substantial agreement between the reviewers on eligibility (Cohen's Kappa = 0.67).

Qualitative studies

Qualitative study findings were analysed following the Joanna Briggs Institute (2014) guidelines. This process involved data extraction, evaluation and synthesis of findings across studies. To conduct the synthesis the author read and reread to identify emergent themes from each study. Findings were grouped into themes based on similarity in meaning. Themes that occurred at least twice across studies were grouped together and presented.

Quantitative studies

There was too much heterogeneity in the factors/variables examined and the method of reporting to combine quantitative study results for statistical analysis (i.e. meta-analysis). Therefore, the current study described and evaluated the reviewed studies, synthesised their data and the direction of relationships were examined and compared to answer the key objectives of the review.

Results

Of 312 citations identified through the initial search, 20 articles met inclusion criteria for review (see Figure 1).

Overall Study Characteristics

Study characteristics are described in Tables 3 and 4. There were more quantitative studies (n= 15) than qualitative (n= 5). All reports of multiple publications were included. Overall, the twenty studies relate to thirteen datasets; seven studies used data from one dataset, another two studies used the same dataset and the remaining eleven studies used separate datasets. All twenty articles were published between April 2013 and October 2017.

Five articles described multinational research; four studies used data from one dataset which was conducted across Brazil, Ecuador, Peru, South Africa, Thailand and the USA and one separate study was conducted across France and Canada. Another twelve were conducted in the USA, two in Thailand (describing research from the same dataset) and one in Africa. Most studies were either RCT's (n=6), open-label longitudinal studies (n=6) or cross-sectional (n=6) in design. One study used data from a dataset with both RCT and open-label components whilst one used a prospective longitudinal cohort design. Across all studies, samples sizes ranged from 24 to 1603 (median; 225.5, inter-quartile range; 50.5-452.5) and overall 6,677 participants were included. Multiple publications were included therefore some participants could have participated in a number of studies. Detailed study characteristics for both qualitative and quantitative studies are described below.

How PrEP adherence was measured

Seven studies measured PrEP adherence through self-report methods. Another four studies measured PrEP adherence through biological methods alone (i.e. plasma blood concentrations, dried blood spots or hair using liquid chromatography/tandem mass spectrometry). Two studies used a combination of self-report and biological methods. One study used electronic pill counts and biological methods whilst another used electronic pill counts and self-report methods. Another two studies measured adherence through a combination of three methods; self-report, biological and pill counts/pharmacy refill dates. Lastly, one study used pill counts alone to determine PrEP adherence. Adherence levels in two studies were not measured.

Levels of adherence across studies

One study reported that at follow-up 17% of TGW and 35% of MSM had protective PrEP levels (i.e. 4 or more doses a week) (Deutsch et al, 2015) whilst another found protective PrEP levels amongst 83.1% and 65.5% of participants at weeks 4 and 48 respectively (Landovitz et al, 2017). Furthermore, one study found 80-86% of participants had protective PrEP levels (Liu et al, 2016) and a sub-study similarly reported participants had protective levels 87% of the time (Gandhi et al, 2017). Parsons et al, (2017) reported that 98% of participants had on average taken four or more doses per week in the last month whilst Parisi et al (2017) stated at the 1-month medical visit 100% of participants had taken four or more doses the week before their medical visit. This decreased to 94.3% at the 3-month visit and increased to 96.6% at the 6-month visit. In one study 86% of participants self-reported they had taken four or more doses per week (Mugo et al, 2015).

Using blood plasma concentrations, one study reported PrEP was detected in 71% of PrEP users (Grant et al, 2014). In longitudinal analysis (i.e. participants with at least two drug levels available), another study found 31% never had drug detected, 30% always had drug detected, and 39% had an inconsistent pattern (Liu et al, 2014).

Of those receiving a PrEP adherence intervention, 90% and 84% of participants achieved 100% adherence at 3-months and 6-months respectively (Mayer et al, 2017). Another study reported that 92.5% of PrEP users took their medication 6-7 days per week (Holloway et al, 2017). However, one study reported that on average only 59% of participants had used PrEP correctly (following an event-based regimen) during their most recent sexual intercourse (Sagaon-Teyssier et al., 2016).

Two studies (using the same dataset) reported that 78% of participants achieved a 'stable' level (i.e. average medication adherence was between 90%-100%), 20% achieved a 'moderate' level (i.e. average medication adherence was between 70%-89%) and 2% achieved 'poor' level (i.e. average medication adherence was between 40%-49%) (Tangmunongvoraul et al, 2013; Tangmunkongvorakul et al, 2016). One study reported that amongst those receiving PrEP, the median number of doses missed (out of possible 30) was 10 (Hosek et al, 2013) whilst another reported that participants did not take their PrEP on 0–1 (33.3%), 2–3 (16.7%), 4–5 (6.6%), 6–7 (23.3%) and 8+ (20%) days over the last 90 days (Storholm et al, 2017). Two studies measured but did not report adherence levels in the sample (Mehrotra et al, 2016; Parker et al, 2015) and in two studies adherence levels were not recorded (Gilmore et al, 2013; Arnold et al, 2017).

Data Synthesis

Factors related to PrEP adherence/non-adherence were extracted from the included studies and grouped into three higher-order categories: individual-level, interpersonal-level and structural-level factors. Individual-level factors describe those that relate to demographic variables (e.g. age, ethnicity, education, location or gender identity), motivation (e.g. attitudes to use PrEP), knowledge (e.g. knowledge regarding PrEP efficacy or use), mental health (e.g. depression) or behaviour (e.g. substance use). Interpersonal-level factors are those that relate to an individual's interaction with others (e.g. enacted stigma or support from others). Structural-level factors relate to concepts in the environment (e.g. access to PrEP or PrEP services) which could influence PrEP use.

Quantitative Studies: Study Characteristics

In total, fifteen qualitative studies were included within the review (please refer to Table 3 for a summary of the included studies).

Five studies reported/used data from the multinational iPrEx study which consisted of a double-blind, randomised, placebo-controlled trial and open-label extension (OLE) (Grant et al, 2010). The open-label cohort trial enrolled MSM individuals previously enrolled in PrEP trials (i.e. iPrEX, ATN 082 and US Safety Study) (Grant et al, 2014). Two studies specifically used data from the double-blinded RCT component; one used data from active-arm participants across all multinational sites whilst another specifically analysed data from the Thailand iPrEX cohort (across both active and placebo arms). Two studies report data based on iPrEx OLE and one study used iPrEx data from both the RCT (active-arm only) and OLE.

Table 3: ***Summary of Quantitative Studies***

Reference	Location	Design	Sample	Measure of adherence*	Analysis
Deutsch et al., 2015	Multinational (Brazil, Ecuador, Peru, South Africa, Thailand and the USA)	Longitudinal, double blinded RCT and open-label study. iPrEx study	339 (RCT) and 192 participants (OLE) TGW Characteristics of RCT (n=339) participants: Age (mean): 26.2 years Ethnicity; Not reported Daily regimen Sampling strategy: Systematic Response rate: RCT- Not reported, OLE- 79%	Biological	Multivariate analysis: yes, Attrition rate: 0%
Gandhi et al., 2017	USA	Longitudinal, open-label study Demonstration project	280 participants, MSM (99%), TGW (1%) Age (range): median 34 years (19–65) Ethnicity; white (78%), Latino (23%), other (Asian, native etc) (13%) and Black (5%) Daily regimen. Sampling strategy: Opt-in design Response rate: 58%	Biological Self-report	Multivariate analysis: yes, Attrition rate: 5%
Grant et al., 2014	Multinational (Brazil, Ecuador, Peru, South Africa, Thailand and the USA)	Longitudinal, open-label cohort study. iPrEx study	1603 participants, MSM (89%), TGW (11%), Age; 18-24 (20%), 25-29 (27%) 30-39 (31%) and >40 (22%) Ethnicity; Latino (72%), Mixed/Other (70%)White (17%), Black (8%), Asian (5%) Daily regimen, Sampling strategy: Systematic Response rate: 62%	Biological	Multivariate analysis; yes Attrition rate: 16%

*Biological methods refers to PrEP drug concentration levels as measured by; blood plasma concentrations, liquid chromatography, tandem mass spectroscopy or dried blood spots or as measured in hair by liquid chromatography or tandem mass spectrometry.

Table 3: ***Summary of Quantitative Studies continued***

Reference	Location	Design	Sample	Measure of adherence*	Analysis
Holloway et al., 2017	USA	Cross-sectional survey	761 participants MSM (97.5%), 'Other' (2.5%) Age; 18-24 (62%), 25-19 (38%), Ethnicity; Hispanic/Latino (32%), White (22%), Black/ African American (25%), Other/mixed (21%) Daily regimen Sampling Strategy: Convenience Response Rate: 43%	Self-report	Multivariate analysis; yes Attrition rate: Not applicable
Hosek et al., 2013	USA	Longitudinal, blinded pilot RCT.	58 participants MSM Age (mean, sd):18-22 years (19.97,1.3), Ethnicity: Black/African American (53%) Native American/Alaskan Native (2%), white (7%), other/mixed race (38%) Daily regimen Sampling Strategy: Convenience Response Rate: 28%	Biological Pharmacy Refill dates Self-report	Multivariate analysis; no Attrition rate: 19%
Landovitz et al., 2017	USA	Longitudinal. open-label, two-arm interventional cohort study	301 participants MSM (n=300), TGW (n=1), Following demographics based on MSM only: Age; 18-25 (12%), 26-35 (46%), 36-45 (24%), 46+ (18%), Ethnicity; White (50%), Hispanic (28%), Black or African American (11%), Asian (6%) and other (5%) Daily regimen Sampling Strategy: Not reported Response Rate: 98%	Biological Self-report	Multivariate analysis; yes Attrition rate: 25%

Table 3: ***Summary of Quantitative Studies continued***

Reference	Location	Design	Sample	Measure of adherence*	Analysis
Liu et al., 2014	Multinational (Brazil, Ecuador, Peru, South Africa, Thailand and the USA)	Longitudinal, double-blinded RCT. iPrEx study	470 participants. Characteristics of active-arm participants (n= 1251): MSM (n= 1088, 87%) TGW (n= 163,13%) Age (years); 18-20 (22%), 21-25 (31%), 26-30 (19%), 31+ (29%). Ethnicity; Mixed race/other (68%), White (18%), Black (9%), Asian (5%). Daily regimen Sampling Strategy; Random and systematic Response rate: 100%	Biological	Multivariate analysis: yes Attrition rate: Unclear
Liu et al., 2016	USA	Longitudinal, open-label study. Demonstration project	557 participants MSM (98.4%) and TGW (1.3%) Age; 18-25 (20%), 26-35 (38%), 36-45 (24%), 45+ (18%) Ethnicity; White (48%), Latino (7%), Black (7%), Asian (5%), Other (6%) Daily regimen Sampling strategy: Systematic and purposive Response rate: 61%	Biological Pill counts Self-report	Multivariate analysis; yes Attrition rate: 22%
Mayer et al., 2017	USA	Longitudinal, open-label pilot RCT	50 participants MSM Age (mean, sd); 38.26 (12.6) years Ethnicity; White (86%), Hispanic/Latino (8%), Other (4%), Black/ African American (2%) Daily regimen Sampling strategy: Convenience Response rate: 98%	Biological Pill counts	Multivariate analysis; yes. Attrition rate: 22%

Table 3: ***Summary of Quantitative Studies continued***

Reference	Location	Design	Sample	Measure of adherence*	Analysis
Mehrotra et al., 2016	Multinational (Brazil, Ecuador, Peru, South Africa, Thailand and the USA)	Longitudinal, open-label study iPrEx study	334 participants. MSM (89%) and TGW (11%) Age: 18-25 years (32%), 26-30 (23%), 31-39 (24%), 40+ (21%). Ethnicity: unknown Daily regimen Sampling strategy: Systematic Response rate: 100%	Biological	Multivariate analysis; yes. Attrition rate: Not applicable
Mugo et al., 2015	Africa	Longitudinal, blinded RCT.	62 participants Age (range): 18-38 years Ethnicity: unknown Daily and event-based regimen Sampling strategy: Systematic Response rate: Not reported	Pill counts Self-report	Multivariate analysis; yes. Attrition rate: 7%
Parisi et al., 2017	USA	Longitudinal, open label study.	171 participants. MSM (n=160), TGW (n= 8), unknown (n=3), Ethnicity; white (60%), black (14%), Hispanic (13%), Asian (9%), other/unknown (4%), Ages; 18-24 (12%), 25-34 years (46%), 35-44 years (19%), 45-54 years (18%), 55+(3%), Daily regimen. Sampling strategy: Systematic Response rate: 100%	Self-report	Multivariate analyses: yes Attrition rate: 51%
Parsons et al., 2017	USA.	Longitudinal, prospective, cohort study.	995 participants MSM Age average (sd): 41.9 years (13.9) Ethnicity: White (72%), Latino (12%), Black (8%), Other/Multiracial (8%) Daily regimen Sampling strategy: Systematic Response rate: Not reported	Self-report	Multivariate analysis; yes. Attrition rate: 5%

Table 3: ***Summary of Quantitative Studies continued***

Reference	Location	Design	Sample	Measure of adherence*	Analysis
Sagaon-Teyssier et al., 2016	France and Canada	Longitudinal, double-blind RCT	400 participants MSM & TGW Age; 18-24 (n=29), 25-29 (n=28), 30-39 (n=72), 40-49 (n=52), 50+ years (n=18). Ethnicity: White (n=183) Event-based regimen Sampling Strategy; Systematic Response rate: 97%	Self-report	Multivariate analysis; yes. Attrition rate: 12%
Tangmunkongvorakul et al., 2016	Thailand	Longitudinal double-blinded RCT. iPrEx study	114 participants, MSM (n=85), TGW (N=29) Age; 18-43 years, Ethnicity; unknown, Daily regimen Sampling strategy- Systematic Response rate- Not reported	Pill counts	Multivariate analysis; no Attrition rate: 0%

Quantitative Data Synthesis

Quantitative findings were extracted from the included studies and grouped into three higher-order categories: individual-level, interpersonal-level and structural-level factors. Across three domains sixteen significant findings emerged across a broader range of other non-significant variables which either facilitated or acted as a barrier to PrEP adherence:

- Age, ethnicity, gender identity, education, location, housing, lifestyle factors; (i.e. travel and lifestyle), regimen, side-effects, substance use, mental health, knowledge, higher levels of HIV risk perception and actual risk behaviour (individual-level factors)
- Sexual behaviour (interpersonal-level factors)
- Financial and adherence intervention (structural-level factors)

The section below describes a description of each category from the reviewed studies.

Individual-level factors

Age

Seven studies reported an association between age and PrEP adherence. Two studies found no significant relationship between age and PrEP adherence (Liu et al, 2016; Mugo et al, 2015). Five studies found a relationship between levels of PrEP adherence and older age (i.e. older individuals were more likely to have protective levels of PrEP (Gandhi et al, 2017; Landovitz et al, 2017; Mehrotra et al, 2016), any drug level detection (Liu et al, 2014) or higher drug concentrations (Grant et al, 2014).

Ethnicity

Four studies found that ethnicity was associated with PrEP adherence. Specifically, three studies found that African-Americans were less likely to have protective PrEP levels than those from any other ethnicity (Gandhi et al, 2017; Landovitz et al, 2017; Liu et al, 2016). However, one study found no significant ethnic differences between those who had initiated PrEP (i.e. gained a prescription) but were not consistently adherent (i.e. taken 4 or more doses a week) compared to those who had initiated and maintained PrEP adherence (Parsons et al, 2017).

Gender identity

Three studies carried out specific analyses examining the relationship between TGW and PrEP adherence. One study found that being TGW was not associated with lower PrEP adherence (i.e. drug detection at week 8 or over time) when compared to MSM (Liu et al, 2014).

Another study found that TGW who used feminizing hormones were less likely to have protective levels or any PrEP drug detection in comparison to TGW who did not use feminizing hormones. However, there was no difference in adherence between TGW who used natural or synthetic oestrogen-based hormones. TGW with the highest risk of HIV (based on sexual practices) were less likely to have PrEP detected. Overall, TGW showed significantly less adherence (regardless of hormone use) than the rest of the MSM population (Deutsch et al, 2015). Lastly, one study found that TGW and MSM adherence was impacted differently by depressive symptoms (please see 'mental health' section below) (Mehrotra et al, 2015).

Education

Six studies reported the relationship between adherence to PrEP and educational level. Four studies found no association between these two factors (Landovitz et al, 2017; Liu et al, 2014; Liu et al, 2016; Mugo et al, 2015). However, two studies found drug concentrations were higher amongst those with a higher educational level (Grant et al, 2014; Mehrotra et al, 2016).

Location

Three studies found that PrEP adherence varied dependent on geographic location (Liu et al, 2014) or was associated with clinic site (Gandhi et al, 2017; Liu et al, 2016). However, after multivariate analyses clinic site no longer stayed significantly associated with adherence in one of these studies (Gandhi et al, 2017). Another study found no significant geographic differences between those who had initiated PrEP (i.e. gained a prescription) but were not consistently adherent (i.e. had not taken 4 or more

doses a week) compared to those who had initiated and maintained PrEP adherence (Parsons et al, 2017).

Housing

Three studies examined the relationship between housing/living situation and PrEP adherence. Two studies found that those with stable housing were significantly more likely to have protective PrEP levels (Gandhi et al, 2017; Liu et al, 2016) whilst another found that living situation or concern about having a place to live was not associated with PrEP adherence (Liu et al, 2014).

Lifestyle factors: travel and lifestyle

Two articles focused on travel and how it related to PrEP adherence. When combining both daily and event-based dosing regimens, one study found frequent travel (i.e. more than three nights on average per week) was significantly associated with lower adherence (Mugo et al, 2015) whilst another found 'being away from home' was one of the most common reasons for missed doses (Hosek et al, 2013). One study found that lifestyle factors were one of the most common reason for missed doses (i.e. being too busy) (Hosek et al, 2013).

Regimen

Only one study examined the relationship between different dosing regimens and adherence. Mugo et al (2015) found that daily versus event-based dosing regimen did not show any significant association with PrEP adherence.

Side Effects

Four studies reported the impact of side effects on PrEP adherence. One study found no association between side effects (i.e. gastrointestinal symptoms or headache) and PrEP adherence (Liu et al, 2014) whilst another reported that only one out of 41 participants who discontinued PrEP stopped because of side effects (Parisi et al, 2017). However, two studies reported that amongst those who discontinued (Holloway et al, 2017) or interrupted their PrEP use (Liu et al, 2016) side effects was the most common reason reported by participants.

Substance Use

Five studies found no significant relationship between alcohol use or drug use and PrEP adherence (Grant et al, 2014; Landovitz et al, 2017; Liu et al, 2014; Liu et al, 2016; Mugo et al, 2015). One study found drug use (i.e. amphetamine use) was significantly associated with adequate PrEP adherence in bivariate analyses but this did not maintain significance in multi-variate analyses (Gandhi et al, 2017).

Mental Health

Only one study examined the relationship between PrEP adherence and mental health. Mehrotra et al (2015) found that pre-existing anxiety was a strong predictor of PrEP adherence. Furthermore, amongst TGW participants, depressive scores above the clinical cut-off (i.e. scores of 16 or more on the CES-D [Center for Epidemiologic Studies Depression Scale] which categorize an individual as ‘at-risk’ of depression (Radloff, 1977)) were associated with decreased PrEP adherence. Amongst MSM individuals, compared to scores below clinical-cut off, scores between 16 and 26 were associated with increased adherence whereas scores of 27 or higher were associated with decreased PrEP adherence.

Knowledge

Three studies commented on the association between PrEP knowledge and PrEP adherence. One study found that answering ‘don’t know’ to a question about belief of PrEP efficacy was associated with PrEP detection at some or all visits, when compared with individuals who never took their PrEP medication (Liu et al, 2014). Another study found “getting questions answered” was a commonly reported reason given by participants when asked what facilitated PrEP use (Parisi et al, 2017). However, one longitudinal study found no significant association between prior PrEP knowledge and adherence (Liu et al, 2016).

Higher levels of HIV risk perception and actual risk behaviour

One study found a relationship between PrEP adherence and greater HIV risk perception (Liu et al, 2014). Three studies reported that self-reported reasons for discontinuing/interrupting PrEP use were: low self-perceived HIV risk (Liu et al, 2016), reductions in HIV risk behaviours (Parisi et al, 2017) or the adoption of other HIV-prevention strategies (Holloway et al, 2017).

Interpersonal-level factors

Sexual behaviour

Nine studies examined the relationship between adherence and sexual behaviour. Six studies highlighted no association between different sexual behaviours and adherence; one found that the number of sexual acts without a condom decreased over the study period but was unrelated to level of adherence (Tangmunkongvorakul et al, 2016). Three studies found that the type of sexual act or partner (Sagaon-Teyssier et al, 2016), the number of sexual partners (Landovitz et al, 2017) and the number of condomless receptive anal sex partners in the last three months (Liu et al, 2014) was not associated with PrEP adherence. Lastly, a study in Kenya also found no significant associations between multiple sexual indicators (i.e. number of sexual partners, any occurrence of sex while drunk, sex with new partner, less than 100% condom use with new or HIV positive partner, receptive anal intercourse or insertive anal intercourse) and adherence (Mugo et al, 2015). One study found that TGW with the highest sexual risk behaviours (i.e. more partners, less condom use and more STI's) were less likely to have PrEP drug detected in blood samples (Deutsch et al, 2015).

Five studies reported significant associations between PrEP adherence and sexual behaviours; four found that two or more condomless anal sex partners in the past 3 months (Liu et al, 2016) or reported condomless receptive anal sex (Gandhi et al, 2017; Grant et al, 2014; Liu et al 2014) was associated with PrEP adherence. Two studies found PrEP adherence was higher amongst participants who had history of a sexually transmitted infections (STI's) or more sexual partners (Grant et al, 2014; Liu et al, 2014). Specifically, individuals who were in a relationship, had any HIV-positive

sexual partners (Grant et al, 2014) or had more male partners (Liu et al, 2014) were more likely to be adherent to their PrEP medication.

Structural-level factors

Financial income and insurance

Four studies (where PrEP was study-funded) found that financial income (Landovitz et al, 2017; Liu et al, 2014; Liu et al, 2016; Mugo et al, 2015) or having financial responsibility for others (Mugo et al, 2015) had no significant association with PrEP adherence. One study found that having health insurance was significantly associated with adequate PrEP adherence (i.e. four or more does a week) (Liu et al, 2016). However, another found that having public or no insurance coverage was not related to protective PrEP levels (Landovitz et al, 2017). One study which examined PrEP use (in a location where PrEP required self-funding) found the second and fifth most reported reasons for discontinuing PrEP were being unable to afford a prescription or the required medical visits for PrEP (Holloway et al, 2017).

Adherence Intervention

One study found that individuals who received a PrEP adherence intervention (i.e. cognitive-behavioural orientated programme which consisted of six nurse-delivered sessions which included: education about PrEP and sexual risk behaviours for HIV and STI's, establishing a regular dosing schedule and discussing the barriers to adherence) had significantly higher levels of PrEP blood plasma concentrations than those who did not at both 3 months and 6 months. However, after completer analyses

(i.e. an analysis where only those who completed the intervention were included), there were no differences between the control and intervention condition (Mayer et al, 2017).

Qualitative Studies: Study Characteristics

In total, five qualitative studies were included within the review (please refer to Table 4 for a summary of the included studies). Four out of five studies were conducted in the USA whilst the remaining study (Tangmunongvoraul et al, 2013) was conducted in Thailand. One study collected data through focus groups and interviews (Gilmore et al, 2013) whilst the remaining four used semi-structured interviews. In total, 182 MSM individuals participated across studies and all studies used a cross-sectional design. Only one study examined a specific MSM subpopulation (i.e. substance-using MSM) (Storholm et al, 2017).

Two studies directly explored the facilitators and barriers to PrEP use (Gilmore et al, 2013; Tangmunongvoraul et al, 2013). One study explored factors which were associated with retention in PrEP care (Arnold et al, 2017) whilst another gained insight into the overall experience of using PrEP amongst MSM (Parker et al, 2015). Lastly, Storholm et al (2017) examined i) how PrEP use affected risk perception and sexual behaviour, ii) facilitators of PrEP adherence, iii) the relationship between adherence and substance use and iiii) the psychosocial impact of PrEP use.

Two studies recruited participants whom were involved in a larger double-blind, randomised, placebo-controlled trial (iPrEx). In one study, iPrEX participants were recruited during their follow-up visit to the sexual health clinic (Tangmunkongvorakul et al., 2013) whilst the other study did not specify how participants (who were enrolled at the iPrEx site) were approached (Gilmore et al, 2013). Three studies recruited participants involved in PrEP programs in outpatient clinics in 'real-life settings' (Arnold et al, 2017; Parker et al, 2015; Storholm et al, 2017). Two studies used a grounded theory approach, one used an adapted grounded theory approach, one used deductive analysis and one used content analysis methods to analyse data. All studies measured PrEP adherence through self-report methods.

Table 4: *Summary of Qualitative Studies*

Reference	Location	Data Collection	Sample	Measure of adherence
Arnold et al., 2017	USA	Semi-structured interviews Grounded theory.	30 participants MSM Age (mean, sd): 18+ years (26.6, 8.2) Ethnicity: Black/African American (n=25), unknown (n=5), Daily regimen Sampling Strategy: Purposive Response Rate: Not reported	Self-report
Gilmore et al., 2013	USA iPrEx study	Focus groups and interviews Deductive analysis	52 participants MSM Age: 22-36 years (median: 43 years) Ethnicity: white (66%), African American (12%), Latino/Hispanic (15%), and Asian (7%), Daily regimen. Sampling strategy: Unclear Response rate: Unclear	Self-report
Parker et al., 2015	USA	Semi-structured interviews Grounded theory.	24 participants MSM Age (mean, sd): 33.2 (10.5) Ethnicity; White (75%), Hispanic/Latino (25%), Other (21%), African American/Black (4%) and Asian (0%), Daily regimen. Sampling strategy: Not reported Response rate: Not reported	Self-report

Table 4: *Summary of Qualitative Studies continued*

Reference	Location	Data Collection	Sample	Measure of adherence
Storholm, Volk, Marcus, Silverberg, & Satre, 2017	USA	Semi-structured interviews Adapted grounded theory approach.	30 participants MSM Age (mean, sd): 20–35 years (27.5, 3.9) Ethnicity; White (40%), Latino (23.3%), Asian/pacific islander (20%) and African-American (16.7%), Daily regimen. Sampling strategy: Purposeful Response rate: Unclear	Self-report
Tangmunkongvorakul et al., 2013	Thailand iPrEx study	Semi-structured interviews and focus groups. Content analysis.	46 participants, MSM (n= 29), TGW (n= 17) Age: 19-37 years Ethnicity: Not reported Daily regimen. Sampling strategy: Purposeful Response rate: 100%	Self-report

Qualitative Data Synthesis

Twenty-six themes were extracted from the included studies and grouped into three higher-order categories: individual-level, interpersonal-level and structural-level factors. Across these three domains seven themes emerged which either facilitated or acted as a barrier to PrEP adherence:

- Substance use, routine and planning, social motivation, side effects and anticipated stigma (individual-level factors)
- Support from others (interpersonal-level factors)
- Finances and access to PrEP-related services (structural-level factors)

Table 5 reports the categories and themes identified across studies with an example quote from the reviewed studies. The table also indicates whether the theme was identified as facilitator or barrier to PrEP adherence. The section below describes a description of each category.

Table 5: ***Synthesis of findings showing common categories and themes identified in the literature.***

Category	Theme	Barrier/ Facilitator	Example
Individual-level factors	Substance Use	Barrier	*"…the biggest reason we forget to take the medicine is from alcohol" (Tangmunkongvorakul et al, 2013; p. 964).*
	Routine and planning	Barrier & Facilitator	*"The only challenge is if I'm going over to a friend's house to stay over for more than a day or going on a vacation where you kinda have to do some planning" (Gilmore et al, 2013; pg 562).* *"I have a little week of pills…whenever it's empty, I refill it, and I keep it on my kitchen counter. And it's kind of, like, right there. I can't escape it" (Storholm et al, 2017; pg. 742).*
	Social Motivation	Facilitator	*"…I know that there is a 50_50 percent chance of having the real drug or placebo. But no matter what I am given, I will continue to take it as advised until the end of the study. Otherwise, there will not be accurate results for the study and for all people" (Tangmunkongvorakul, 2013; p. 962)*
	Side effects	Barrier	*"…The only side effect that I experienced was a bad headache when I first started takin' it, and being nauseous. It lasted for the whole day. After I took PrEP the first time I stopped" (Arnold et al, 2017; p.5).*
	Anticipated Stigma	Barrier	*"I take [the pill] in private 'cause I have friends that's HIV negative and homophobic or positive-phobic and I know who those friends are so I just be real particular where I take my pills at" (Gilmore et al, 2013; pg.562).*
Interpersonal-level factors	Support from others	Barrier & Facilitator	*"I was worried it might upset my partner that I was taking it because you should trust each other." Arnold et al, 2017; p.5).* *"I think just having the human contact once a month of just having a counsellor and just sort of check in and think about behaviors and things like that. I think that had a really good impact" (Gilmore et al, 2013; p.962).*
Structural-level factors	Financial	Facilitator	*"…I wouldn't pay more than fifty dollars. I probably would not be able to afford to pay out of pocket" (Arnold et al; 2017; p.4).*
	Access to PrEP-related services	Facilitator	*"…I know that we are guinea pigs. Nobody has done this kind of research before. But I feel that the compensation such as health check-ups, free medical services and money are worthwhile…" (Tangmunkongvorakul et al, 2013; p. 963).*

Individual-level factors

Substance Use

Two studies identified substance misuse as a barrier to PrEP adherence (Storholm et al, 2017; Tangmunkongvorakul et al, 2013). Both studies highlighted the use of alcohol as a barrier to consistent medication use. One study reported the significant negative impact drug use (i.e. methamphetamine and poly-substance drug use) had on their routine and subsequently their PrEP adherence (Storholm et al, 2017).

Routine and planning

Three studies identified routine as a factor which was related to PrEP adherence and non-adherence. All studies highlighted that having a routine facilitated consistent PrEP use. One study highlighted the role of reminders (e.g. use of phone alarms) as part of this established routine (Storholm et al, 2017). Two studies highlighted that established medication management skills (i.e. pre-existing routines for other medications) facilitated PrEP adherence (Gilmore et al, 2013; Tangmunkongvorakul et al, 2013). The same two studies also highlighted changes in routine (e.g. travel, having a busier schedule than usual, going out or staying somewhere else) contributed to missed PrEP doses.

Social Motivation

Two studies discussed that amongst MSM participants the personal sense they were "giving back to the community" acted as a motivating factor which facilitated PrEP adherence. In this sense, adherence was equated with study participation. By participating (and adhering well) participants had a sense they were contributing to results which could benefit their social group (Gilmore et al, 2013; Tangmunkongvorakul et al, 2013).

Side Effects

Two studies reported on the role of side effects which acted as a barrier to PrEP adherence. Both studies highlighted that anticipated side effects could undermine PrEP use. One study acknowledged that actual or perceived side effects of PrEP stopped PrEP use (Arnold et al, 2017). The other study highlighted that medicine concerns were exacerbated due to the uncertainty of PrEP or placebo use amongst participants. This meant that MSM participants felt non-adherence was more permissible (Tangmunkongvorakul et al, 2013).

Anticipated stigma

Three studies reported that stigma was a factor that acted as a barrier to PrEP adherence (Arnold et al, 2017; Gilmore et al, 2013; Tangmunkongvorakul et al, 2013). Across studies, MSM participants reported anticipated stigma in different domains (i.e. homophobia, being classed as HIV positive or sexually promiscuous) by friends, family or religious communities. Efforts to avoid this stigma (e.g. not carrying or taking PrEP in certain situations) acted as a barrier to adherence.

Interpersonal-level factors

Support from others

Three studies highlighted that support from others helped promote PrEP adherence. One study also highlighted that lack of support from family and friends could act as a barrier to PrEP adherence (Arnold et al, 2017). For example, when PrEP use was not supported by primary sexual partners (i.e. participants reporting anticipated or actual conflicts within the relationship) this would act as a barrier to PrEP use. However, supportive relationships with friends and family increased confidence in taking PrEP and promoted daily PrEP use (Arnold et al, 2017; Gilmore et al, 2013; Tangmunkongvorakul et al, 2013). Two studies reported that supportive, non-judgemental relationships with healthcare staff promoted PrEP adherence. Within each study, one dimension of this relationship with staff involved counselling, where the facilitators and barriers to PrEP adherence were discussed (Gilmore et al, 2013; Tangmunkongvorakul et al, 2013).

Structural-level factors

Financial

Two studies reported that access to financial support facilitated PrEP use. Both studies highlighted that participants could access financial support to help with PrEP costs which allowed ongoing PrEP use (Arnold et al, 2017; Parker et al, 2015).

Access to PrEP-related services

Two studies reported that access to other PrEP-related services facilitated PrEP use. By using PrEP, participants reported also having access to other facilities such as HIV and STI testing, health monitoring and physical examinations (Gilmore et al, 2013; Tangmunkongvorakul et al, 2013).

Methodological Quality

The methodological quality of both quantitative and qualitative studies is summarised in Table 6 and 7 respectively. A cross (x) indicates that the criterion was either not met or it was unclear if the criterion was met.

Quantitative studies: Methodological Quality

External Validity

Eleven of the fifteen quantitative studies clearly reported that a convenience sampling strategy was not used. Six studies reported good response rates, that is, at least 80% of those eligible to participate were recruited. Only four studies met both criteria for external validity.

Internal Validity

Eleven out of fifteen studies measured adherence objectively, using biological methods (i.e. plasma blood concentrations, dried blood spots or hair using liquid chromatography/tandem mass spectrometry) and/or pill counts. All but three studies, reported the number of withdrawals across the study. Ten studies were free of attrition bias, reporting that at least 80% of those invited to participate in the study were included in the final analysis. All fifteen studies measured potential confounding variables and all but two studies carried out multivariate analyses to control for potential confounding variables. In total, only two of the 15 studies provided evidence of meeting all criteria for internal validity.

Qualitative studies: Methodological Quality

All studies met all criteria for credibility, three out of five studies met transferability criteria whilst no study met the criteria for confirmability as no study detailed/considered the researcher's influence on study findings.

Table 6: ***Methodological quality ratings for quantitative studies***

References	External validity			Internal validity				
	Representativeness of the sample for the target population	The percentage of selected individuals who agreed to participate		Objective measurement of data collection methods	Number of withdrawals	Percentage of participants included in final analysis	Extent to which possible confounding variables were measured	Extent to which possible confounding variables were analysed
Deutsch et al., 2015	✓	X		✓	x	✓	✓	✓
Gandhi et al., 2017	✓	X		✓	✓	✓	✓	✓
Grant et al., 2014	✓	X		✓	✓	✓	✓	✓
Holloway et al, 2017	x	X		x	✓	✓	✓	✓
Hosek et al., 2013	x	X		✓	✓	✓	✓	x
Landovitz et al., 2017	x	✓		✓	✓	x	✓	✓
Liu et al., 2014	✓	✓		✓	✓	x	✓	✓
Liu et al., 2016	✓	X		✓	✓	x	✓	✓
Mayer et al., 2017	x	✓		✓	✓	x	✓	✓
Mehrotra et al., 2016	✓	✓		✓	x	✓	✓	✓
Mugo et al., 2015	✓	X		✓	x	✓	✓	✓
Parisi et al., 2017	✓	✓		x	✓	x	✓	✓
Parsons et al., 2017	✓	X		x	✓	✓	✓	✓
Sagaon-Teyssier et al., 2016	✓	✓		x	✓	✓	✓	✓
Tangmunkongvorakul et al., 2016	✓	X		✓	✓	✓	✓	x

Table 7: ***Methodological quality ratings for qualitative studies***

References	Credibility		Transferability	Confirmability
	Clarity of data collection and analysis	Representativeness of the data	Are the findings transferable to other settings	Is the analysis grounded in the data? Is appropriate consideration given to how the findings relate to researchers' influence?
Arnold et al., 2017	✓	✓	✓	x
Gilmore et al., 2013	✓	✓	x	x
Parker et al., 2015	✓	✓	x	x
Storholm, Volk, Marcus, Silverberg, & Satre, 2017	✓	✓	✓	x
Tangmunkongvorakul et al., 2013	✓	✓	✓	x

Discussion

Overview of Study Findings

This review aimed to synthesise the factors related to PrEP adherence amongst MSM. Twenty studies were included and across studies twenty factors were measured and analysed in relation to PrEP adherence. Eleven out of twenty factors produced inconsistent findings across studies. Most discrepancies were not due to differences in methodological design (e.g. whether blinded RCT or longitudinal open-label design), study location or sample size. The key findings from each higher-order category (i.e. individual, interpersonal and structural-levels) and their relation to previous reviews and theory will be discussed below:

Individual-level factors

Individual-level factors were the most commonly measured variables to examine in relation to PrEP adherence (n=16). Nine variables produced inconsistent findings across studies. The majority (six out of eight studies) found no relationship between alcohol or drug use and PrEP adherence. This is inconsistent with reviews and meta-analyses that highlight substance use as a barrier to ART adherence (Mills et al, 2006; Hendershot et al, 2009). The Information-Motivation-Behavioural Skills (IMB) model, a theoretical model of adherence behaviours, proposes that situational variables such as substance use can act as a moderating factor to adherence behaviours. The model proposes that substance use could moderate the relation between IMB model constructs and adherent behaviours (Fisher, Fisher, Amico & Harman, 2006). Importantly, the theory specifies that the impact of these factors varies dependent on the level/intensity of the moderating factor. Therefore, inconsistent review findings may

reflect differences in the definitions and levels of substance use across studies which could have impacted PrEP adherence differently.

Most findings (five out of eight studies) suggested a relationship between older age and PrEP adherence. This is consistent with the ART adherence literature where a meta-analysis found older adults are less likely to be non-adherent than younger HIV-positive individuals (Ghidei et al 2013). This finding is different to reviews focused earlier in the prevention cascade which found younger age was predictive of higher acceptance of PrEP (Peng, Su, Fairley, Chu, Jiang, Zhuang & Zhang, 2017). It may be that there are different predictors at different stages of the PrEP cascade. The health belief model (HBM) is a value expectancy theory designed to predict health behaviours (Rosenstock, 1974). The model theorises that individual characteristics such as age are "modifying variables" which can indirectly impact health behaviours (i.e. adherence) by affecting a person's beliefs about the perceived seriousness, benefits and barriers to action. This suggests that older-age PrEP users may have different beliefs from younger MSM users that may help to facilitate PrEP adherence. Future research could explore age-related beliefs that may be associated with PrEP adherence.

Four of six studies reported a relationship between anticipated or actual side effects and less PrEP adherence. This has been echoed by both reviews earlier in the prevention cascade examining willingness and barriers to hypothetical PrEP use (Koechlin et al, 2017) as well as within the ART adherence literature (Al-Dakkak et al, 2013). The safety profile of PrEP is high and side effects have shown to be in most cases mild, short-term (e.g. headaches) and/or reversible (Mugwanya & Baeten 2016).

This suggests that participants may not have had accurate information/support available in which to contextualise their anticipated or actual experience of PrEP side-effects, which may have impacted their adherence. The IMB model of ART adherence theorises that individuals perceived or objective ability to minimise side-effects is one of many behavioural skills which can directly influence adherence behaviour.

Three studies reported that participants felt that having an established routine and planning (i.e. use of reminders) facilitated PrEP adherence. Furthermore, studies found that lifestyle factors (i.e. frequent travel and busy lifestyle) were all associated with less PrEP adherence. This is consistent with studies using HIV-positive individuals which found lifestyle factors (e.g. changes to daily routine or being away from home) may negatively influence ART adherence (Shubber et al, 2016). Overall, this highlights that lifestyle factors which may vary over time may influence PrEP adherence in particular contexts. This finding is consistent with the IMB model of ART adherence which postulates perceived and objective behavioural skills (e.g. the ability to incorporate PrEP into everyday life, self-cue and self-administer PrEP) are the critical prerequisite for adherence for occur (Fisher, Amico, Fisher & Harman, 2008).

All three studies supported that higher levels of HIV risk perception and risk behaviour were related to PrEP adherence. This suggests that PrEP use may be related to MSM individuals' perceived risk or actual episodes of high-risk sexual behaviour. Koechlin et al (2017) also found that across risk groups low HIV risk perception acted as a barrier to hypothetical PrEP use. Risk perception is central to many health-specific behavioural theoretical models including the HBM model (Rosenstock, 1974), protection motivation theory (Rogers, 1975) and the extended parallel process model

(Witte, 1992). Consistent with current findings these theories suggest that an individual's perceived susceptibility to a threat (e.g. the perceived likelihood of HIV acquisition) shape health behaviours (e.g. PrEP adherence).

The review found a relationship between ethnicity and less PrEP adherence. Three out of four studies found African-Americans were less likely to be adherent than those from any other ethnicity. The one study which did not find this relationship had a very small sample size and therefore may have not have had the power to detect this finding (Parsons et al, 2017). Black MSM are disproportionately affected by HIV in the USA and disparities in physical health access and outcomes has been widely documented (relative to other ethnic groups) (Wheeler et al, 2016). The current review is consistent with a meta-analysis which found black HIV-positive US MSM were less likely to adhere ART than MSM from any other ethnicity (Millett et al, 2012). This suggests that African-American MSM may be less likely to adhere than other ethnic groups, and may require additional clinical adherence support. Akin to age, the HBM model theorises that ethnicity is another modifying variable which can indirectly impact health behaviours (i.e. adherence). This suggests that PrEP users from different ethnic groups may have different beliefs which may impact adherence differently. Future research could also explore beliefs held by different ethnic groups that may be associated with PrEP adherence.

One finding related to housing differed across methodological design; two open-label studies (one of which was a sub-study of the other) reported stable housing was associated with PrEP adherence whereas a study using a blinded RCT design found no association. The blinded RCT may have had more staff resources to promote

adherence in the study (e.g. consistent outreach) than the open-label demonstration projects reflecting 'real-life' resource settings (Patel et al, 2017). Therefore, aspects of the RCT design could have acted as a confounding variable to PrEP adherence and could explain why housing was not found to be significantly related to PrEP adherence in the blinded RCT study. A meta-analysis found a positive significant association between housing stability and ART medication adherence amongst HIV-positive individuals (Harris, Xue & Selwyn, 2017). This finding is consistent with research that has found lifestyle factors and routinization of daily activities were related to ART adherence (Wagner & Ryan, 2004). Housing stability could impact the extent to which an individual's daily life has structure and routine and this may play a role in PrEP adherence. Theoretically, akin to substance use, housing stability is described as a moderating factor to adherence in the IMB model.

Three studies found anticipated stigma (i.e. homophobia, being classed as HIV positive or sexually promiscuous) by friends, family or religious communities was reported to be a barrier to PrEP adherence. This is consistent with Peng et al's (2017) review that found MSM with low perceived stigma from friends, society and healthcare providers about PrEP use were more likely to accept PrEP as a preventative healthcare intervention. Furthermore, a meta-analysis found that HIV stigma (i.e. both anticipated and enacted) negatively influences ART adherence (Langebeek et al, 2014). The IMB model that states that an individuals' social motivation (i.e. perceived social pressure from friends, family and healthcare providers) can influence behavioural skills and adherence behaviour.

Interpersonal-level factors

Eleven studies examined the relationship between interpersonal-level factors and PrEP adherence. Six studies found a relationship between PrEP adherence and sexual behaviour (i.e. indices of increased HIV sexual risk behaviours amongst MSM were associated with PrEP adherence). As highlighted above, risk perception is a core component of many theoretical models to explain health behaviour. The HBM model (Rosenstock, 1974) theorises that an individuals' risk perception is in part determined by their perceived susceptibility of harm. Therefore, findings that increased sexual-risk behaviour was related to PrEP adherence may be explained by increased HIV risk perception (i.e. increased sexual-risk behaviour increases HIV risk perception).

Three studies identified that support from others (i.e. friends, family and healthcare staff) was a factor that was perceived to be related to PrEP adherence. This is consistent with review findings examining factors that facilitated PrEP use amongst hypothetical PrEP users as well as ART adherence amongst HIV-positive individuals (Ammassari et al, 2002; Koechlin et al, 2017). Furthermore, this finding is consistent with the IMB model that states that an individuals' social motivation (i.e. perceived social pressure from friends, family and healthcare providers) can influence behavioural skills and adherence behaviour.

Structural-level factors

Nine studies examined the relationship between structural-level factors and PrEP adherence. The review found that (where PrEP was study-funded) financial income was not related to adherence. However, one study (where PrEP was self-funded) showed that financial reasons were the main reason for discontinuation. Studies supported that PrEP adherence was facilitated by financial support and access to PrEP-related services. This finding is consistent with previous reviews that reported cost and affordability were barriers to willingness/acceptability and uptake of PrEP (Koechlin et al 2017; Peng et al, 2017). Theoretically, the IMB model conceptualises poor access to healthcare as a key moderating factor which can directly influence adherence behaviours. It highlights that the increased barriers to healthcare access adherence will be difficult regardless of an individual's information, motivation or behavioural skills (Fisher & Fisher, 2002). Access to PrEP is context-specific, highly variable and ever-changing. These findings highlight that in locations where PrEP or PrEP-related healthcare services are not easily accessible then PrEP adherence and effectiveness could suffer.

Strengths and Limitations of the Review

One of the main strengths of the review was its broad inclusion criteria. This was reflected in a comprehensive search strategy which included peer-reviewed journals with no regional restrictions. However, the search was restricted to English-language publications and no grey literature search took place. This could have decreased the sensitivity of the search and likelihood that all relevant studies were included. A strength of the current review process was that two researchers conducted the eligibility assessment for study inclusion and performed an assessment of bias upon the included studies. This reduced the possibility of the exclusion of relevant studies and provided inter-rater reliability for assessments made (Liberati et al, 2009).

A limitation of the review was that there was overlap in participants across studies due to several studies reporting findings from the same dataset/trial. This lowers the variability and power of the review findings and may lead to over-interpretation of the findings. Another limitation of the review related to the grouping of independent variables which showed considerable heterogeneity in the measures and definitions used. Although there was overlap in the description of the synthesised constructs (e.g. substance use) the variability described may have impacted the internal validity of findings. Furthermore, this variability meant that it was not possible to carry out meta-analysis limiting the substantiality of conclusions drawn. The inability to do this meant the current review findings have limited power as pooled estimates of effect size could not be identified, disagreements between study findings could not be resolved and moderation analysis could not take place. Additionally, potential publication bias was not assessed which could have impacted the interpretation of study findings.

Strengths and Limitations of the Included Studies

A major limitation of the included studies regarded the varied definitions and tools used to measure adherence. Furthermore, there was large variability in the factors measured and analysed in relation to PrEP adherence across studies. This inconsistency makes synthesis and interpretation of the relationship between variables and PrEP adherence difficult.

A third limitation was that studies did not document key behavioural context/factors which may have impacted adherence. For example, most studies did not record whether non-adherent episodes occurred within periods of risky sexual behaviour. This is crucial as periods of non-adherence in context of no sexual behaviour equates to low risk**.** By failing to conceptualise behavioural factors study findings are limited in how much they can inform knowledge regarding the relationship between these factors and adherence (van der Straten et al, 2012).

Most studies have used between-participant correlates of PrEP adherence (e.g. ethnicity) to make comparisons between 'good-adherers' and 'poor-adherers'. Such designs prevent investigation of the factors related to variability in adherence across situations within an individual. This is important because individuals may go through phases of taking and intentionally or unintentionally skipping their medication (WHO, 2003). The review highlights that many factors that relate adherence could be situationally-specific (e.g. changes in routine). As research did not examine factors related to specific adherent/non-adherent episodes these relationships went undetected.

A strength of the included studies was that the majority used a longitudinal design which allowed researchers to detect adherence over time and the overall range of designs used across studies increased the generalisability of findings (Caruana et al 2015). However, the use of RCTs (n=6) limits the generalisability of findings. For example, the increased resources available within RCT designs (e.g. increased monitoring) differ from what can be offered in real-life clinical settings. This means that these designs may overestimate PrEP adherence and when implemented in real-world setting predictors of adherence may differ (Amico, 2012). Alongside this, participants whom were recruited to RCT's may not be representative of the general PrEP taking population (e.g. they may be more motivated to engage in preventative strategies). Lastly, most studies were conducted in large urban cities which may impact the generalisability of findings to other regional areas.

Theoretical Implications

The studies included in the review did not use theory to choose variables to measure in relation to PrEP adherence. As a result of this, research has not concluded whether a specific theoretical model accurately explains PrEP adherence. The current review highlights that the theoretical development to understand PrEP adherence requires a model which incorporates multi-faceted components which may impact an individuals' PrEP-taking behaviour. For example, the review highlights the potential utility of the theories such as the Information-Motivation-Behavioural Skills Model (IMB) (Fisher et al, 2006) to understand PrEP adherence. The IMB model, describes behavioural and psychological determinants of adherence-related behaviours (Fisher et al, 2006). The model recognises three individual constructs; information, motivation and behavioural skills which are needed for an individual to engage in a health behaviour (i.e. successful adherence) (Deakin et al, 2005; Fisher et al, 2006). The model also incorporates moderating factors which affect adherence including; psychological health, living situation, access to medical care and substance use (Amico et al, 2009). This model has been specifically adapted to explain antiretroviral adherence (Fisher et al, 2006) and given the overlap between predictors of PrEP and ART adherence highlighted above may have relevancy. Furthermore, the IMB model, describes a broad range of determinants of adherence as well as moderating factors which may be better placed to acknowledge the potentially situationally-specific and complex factors involved in PrEP adherence highlighted above (Amico et al, 2009).

Research Implications

There were equal numbers of studies with a RCT and longitudinal open-label design. It is important future studies continue to examine the use of PrEP within real-world settings (e.g. in settings with typical resources for that location) to improve the external validity of findings. Notably, most studies were conducted in urban cities and only one study was conducted within a European country. Future research needs to continue to examine PrEP adherence amongst diverse populations and implementation settings to increase the generalisability and examine any cross-cultural differences in factors related to PrEP adherence. Lastly, research within diverse populations (e.g. TGW) and within MSM sub-populations (e.g. black and ethnic minority and older-aged MSM) would be useful to delineate specific facilitators/barriers to PrEP use and to inform individualised PrEP adherence interventions.

As mentioned above, an important limitation was that studies reported adherence but did not record key behavioural context/factors which may have impacted adherence. Future research should report these variables (e.g. whether sex occurred) over periods of adherence/non-adherence to better understand patterns of adherence. It would also be useful if studies examined the role of situationally-specific factors using within-participant research which would allow more confident causal inferences to be made between potential adherence determinants and medication use. Furthermore, development and use of standardised assessment tools to measure variables related to PrEP adherence and standardised definitions of adherence could improve the inconsistency and variability across studies. If future studies used a standardised definition of ‘adequate adherence’ and measured key behavioural/contextual factors this would allow recognition of factors related to clinically significant non-adherence.

This standardisation would also facilitate synthesis across studies and allow meta-analysis to be performed.

Practice Implications

Due to the limitations highlighted above, the practical implications of the review are limited/expressed cautiously. At most, the review can suggest variables that could be targeted in interventions. The review highlights the need for tailored PrEP adherence interventions which address the wide-ranging facilitators and barriers to PrEP adherence which may vary dependent on an individual's situation. Crucially, the review has highlighted potentially modifiable factors (e.g. routine and planning) which could be targeted within PrEP adherence interventions as well as used to identify those most 'at-risk' of non-adherence. The finding that PrEP adherence may be impacted by anticipated or actual side effects as well as perceived or actual periods of low HIV risk highlights the importance of PrEP psycho-education. This would be crucial to contextualise and manage PrEP side-effects and ensure that situations that individuals perceive as low-risk for HIV acquisition correspond to actual low risk. Overall, this is consistent with WHO PrEP implementation guidelines (2017) that clinicians should support adherence by discussing, how to incorporate PrEP into daily routine, side-effects and how to plan PrEP discontinuation safely.

The review highlights the importance of support from others, including healthcare staff, which may facilitate adherence. Review findings support WHO guidelines (2017) that during PrEP follow-up appointments clinicians discuss potential stigma from others, show professional support of PrEP as a responsible choice and advocate disclosure of PrEP use to someone they trust so that they can offer support. The provision of

education and information (e.g. educational media campaigns in the general population) may be useful at a wider societal level to help facilitate support and reduce perceived stigma. The structural-level factors identified highlight that accessibility to PrEP may play an important role in PrEP adherence. This suggests that commissioners should consider the potential implications of financial barriers on the effective implementation of PrEP and thereby the reduction of HIV acquisition. Decisions to not make PrEP more widely accessible given the cost of this initiative must be balanced against the economic implications of potential lifetime adherence to ART medications.

Psychological and behavioural within-participant predictors of adherence to oral HIV Pre-Exposure Prophylaxis (PrEP)

Abstract

Pre-Exposure Prophylaxis (PrEP) is a safe and efficacious HIV prevention tool. When adhered to, if HIV exposure occurs, this antiretroviral drug stops the virus entering cells and replicating (i.e. the person remains HIV negative). The effectiveness of PrEP is variable, however, explained by differences in PrEP adherence. PrEP adherence is often inconsistent *within* individual, whereas most studies only investigate adherence *between* individuals. Understanding psychological and behavioural correlates of PrEP adherence is important to develop effective adherence interventions. This study investigated within-participant behavioural and psychological differences between adherent and non-adherent PrEP episodes in men who have sex with men (MSM), informed by theory (the Information-Motivation-Behavioural Skills model). Sixty-seven HIV-negative MSM at high-risk of HIV acquisition were recruited from two London sexual health clinics. All participants had followed a daily dosing PrEP regimen for at least three months and had shown inconsistent adherence in the previous month. Participants completed a questionnaire measuring psychological and behavioural variables for both an adherent and non-adherent episode. Paired t-tests, McNemar's chi-square tests and a conditional logistic regression (CLR) model were used to analyse associations between behavioural and psychological factors related to adherent and non-adherent events. Lower reported information about PrEP, lower behavioural skills related to PrEP use and lower positive affect were associated with non-adherent episodes. There were no significant differences in negative affect or PrEP motivation between episodes. A CLR model including information, behavioural skills and positive affect was significantly predictive of non-adherent episodes, although only behavioural skills was statistically significant independently. Behavioural factors including weekend days, lack of reminders, non-normality of the day, being out

of the home, not being alone and substance use were also associated with PrEP non-adherence. Findings suggested that situational psychological factors are important for PrEP adherence. Adherence interventions should consider focusing on potentially modifiable situational variables (psychological and behavioural).

Introduction

HIV and Pre-exposure Prophylaxis (PrEP): General Overview

The introduction and dissemination of antiretroviral therapy (ART) has meant that HIV (Human Immnodeficiency Virus) has transitioned from being a fatal illness to chronic healthcare condition (Montaner et al, 2014). HIV has lifelong treatment implications and represents a burden for people with HIV (e.g. coping with HIV stigma and medication side effects) as well as being associated with significant healthcare costs (Laryea & Gien, 1993; Nakagawa et al, 2015).

Globally, 36.7 million people were estimated to be living with HIV in 2016 (UNAIDS, 2017). The prevalence of HIV varies across countries and population subgroups (UNAIDS, 2016). The United Kingdom (UK), considered as having a 'concentrated' epidemic (i.e. where HIV has spread rapidly within specific sub-populations but is not well-established in the general population), had an estimated 101,200 people living with HIV in 2015 and approximately 6,095 of these people were newly diagnosed in the same year (Public Health England (PHE), 2016; Wilson & Halperin, 2008). Despite various HIV prevention initiatives (e.g. increased HIV testing and earlier initiation of ART which can reduce HIV's infectiousness) between 2000 to 2013 HIV incidence rates remained relatively stable in the UK (Aghaizu et al, 2016; Birrell et al, 2013; Phillips et al, 2013). However, recent data indicates that incidence rates have decreased particularly in those deemed most at risk in the UK; gay, bisexual and men who have sex with other men (MSM) (Aghaizu et al, 2016; PHE, 2017). This shift has been attributed to combined preventative strategies (i.e. increased HIV testing, earlier initiation of ART) which includes access to the newer initiative of oral pre-exposure prophylaxis (PrEP) (Brown et al, 2017).

PrEP involves people who are HIV-negative taking an antiretroviral drug. Specifically, those containing both tenofovir disoproxil (TDF) and emtricitabine (FTC) are currently recommended for all people at substantial risk of HIV infection (i.e. populations with an HIV incidence of about 3 per 100 person-years or higher) (WHO, 2016). When taken daily, it takes up to seven days for there to be high enough drug concentrations in a HIV negative MSM individual's bloodstream, genital tract and rectum for PrEP efficacy. If HIV exposure then occurs, this antiretroviral drug stops the virus entering cells and replicating (i.e. the person remains HIV negative) (Seifert et al, 2014). Consistent with British HIV Association guidelines (McCormack et al, 2016b), UK health care services advise MSM at high-risk of HIV acquisition one of two dosing regimens;

1) Daily regimen; one tablet taken every day. Research suggests that for PrEP to be effective MSM sexually active individuals need to take at least four doses a week regardless of sexual activity levels (Grant, 2014).
2) Event-based regimen; two doses of PrEP between two and twenty-four hours before sex, a third dose twenty-four hours later and a fourth dose forty-eight hours later (Molina, 2015).

PrEP differs from post-exposure prophylaxis (PEP) where ART medication is taken after a recent possible exposure to HIV has occurred. In these emergency situations, PEP is initiated within 72 hours and continued for a 28-day course (Young, Arens, Kennedy, Laurie & Rutherford, 2007).

The safety and biological efficacy of PrEP to prevent HIV acquisition has been demonstrated by placebo-controlled trials within MSM and heterosexual samples (Grant et al, 2010; Grant et al, 2014; Baeten et al, 2012; Molina et al, 2015; McCormack et al, 2016a; Thigpen et al ,2012; Choopanya et al, 2013). However, when implemented PrEP has shown wide ranging effectiveness in relation to HIV prevention relative to placebo ranging from -49% to 86%. These wide-ranging results have been explained by varied adherence (Van der Straten et al, 2012; Fonner et al, 2016). Studies using MSM samples found that between 16-43% of participants did not take their PrEP as prescribed (Molina et al, 2015; McCormack et al, 2016a; Mayer et al, 2014) whilst others have reported that 27-66% of MSM participants did not have drug levels needed for PrEP effectiveness (Cohen et al, 2014; Hosek et al, 2017). For a detailed description of studies which have examined PrEP effectiveness and MSM adherence please refer to pages 21-24. Overall this literature has highlighted that the implementation of PrEP as a prevention strategy must be considered as bio-behavioural due to the factors (i.e. adherence) that moderate its efficacy (Kippax & Stephenson, 2012). Understanding the predictors of PrEP adherence/non-adherence is crucial to the development of a theoretical framework and tailored adherence interventions. The systematic review presented earlier in this thesis synthesised the literature examining factors related with PrEP adherence amongst MSM who had access to PrEP or had been part of a placebo arm in a randomised control trial (RCT) where the active arm took PrEP medication. This highlighted various factors such as older age, stable housing, higher levels of HIV risk perception and actual risk behaviours, routine and planning, lifestyle factors (i.e. less travel and being less busy), less anticipated stigma, not being African-American, less anticipated or actual side-effects and support from others were related to PrEP adherence.

Critique of existing literature

Measures of adherence and behavioural factors

Unfortunately, there has been heterogeneity in how adherence in context of a daily dosing regimen has been defined (e.g. one missed dose or over three missed doses being described as non-adherence) and captured (e.g. use of self-report or biological methods). Furthermore, there has been large variability in the factors measured and analysed in relation to PrEP adherence across studies. Altogether, this makes synthesis and interpretation of the relationship between factors related to PrEP adherence difficult. A second limitation (regardless of how adherence was defined/measured), was that studies have not documented key behavioural context/factors which may have impacted adherence/non-adherence. For example, research has not recorded whether non-adherent episodes occur within periods of risky sexual behaviour. This is crucial as periods of non-adherence in the context of no sexual risk behaviour equates to low risk of HIV acquisition**.** By failing to conceptualise both behavioural factors and biological measures of adherence, these studies have been unable to inform knowledge regarding patterns of adherence as significantly as they could (van der Straten et al, 2012).

Study Design and within-participant research

Due to the different study designs used it is difficult to decipher the generalisability of findings. For example, blinded trials may report lower adherence levels because participants are aware that they may be receiving an ineffective placebo (Underhill, 2011). However, well controlled RCT trials may also overestimate adherence due higher levels of monitoring (Amico, 2012). Adding to the difficulty in understanding

adherence is the fact that research describes between-participant' correlates of PrEP adherence relating to variables such as HIV stigma, ethnicity and age (e.g. Mehrotra et al., 2016; Liu, 2015). This is where comparisons are made between 'good-adherers' and 'poor-adherers'. Such designs prevent investigation of other factors related to variability in adherence across situations within an individual. This is important because individuals often intentionally or unintentionally skip their medication. For example, WHO (2003) highlighted 40-50% of individuals across medical conditions were inconsistently adherent and similarly, PROUD showed 40% of MSM participants did not take their PrEP medication 100% of the time and 36% intentionally did not adhere for a period (McCormack et al, 2016a).

An alternate approach to examining adherence is to assess situational factors that are associated with specific episodes of medication use/non-use. Through this investigation, factors which may vary according to specific contexts for example, affect, behaviour and cognition, can be investigated whilst static demographic factors are controlled for (Wagner & Ryan, 2004). This approach allows more confident causal inferences to be made between potential adherence determinants and medication use than a between-participants design.

There are no known published reports of episodic level adherence of PrEP in HIV negative individuals at high-risk of HIV transmission. However, research has shown the possibility of examining a number of episodes using a within-individual approach across a period of time to investigate predictors of ART adherence (Cook, Schmiege, Bradley-Springer, Starr & Carrington, 2017). Research using this ecological momentary assessment (EMA) methodology (e.g. daily diaries) allows measurement of the variable under investigation close to its actual occurrence, however, is limited in the amount of information obtained. Furthermore, evidence of this episodic-level

variation has been seen within Hawkins et al (2016), a quantitative study, which explored ART adherence in young adults with perinatally-acquired HIV. This study found there were variables significantly associated with non-adherence within the same person across different episodes for example, lower levels of positive affect and lower levels of behavioural skills. Additionally, Vosper, Evangeli, Porter & Shah (in press) examined within-participant correlates of oral chelation adherence on a daily (episodic) basis amongst those with the life-long health care condition Beta-Thalassaemia-Major. This study found that situationally-specific factors (i.e. higher self-efficacy) significantly predicted adherent episodes. Both studies highlight important behavioural and situationally-specific predictors of adherence within populations where medication is used for treatment. Situationally-specific factors could be explicitly explored within the HIV negative PrEP population where medication is used for primary prevention where predictors may differ (Marcus et al, 2014).

The Information-Motivation-Behavioural Skills Model (IMB)

The review highlighted that studies did not use theory to select variables to measure in relation to PrEP adherence. Research has not concluded whether a specific theoretical model accurately explains PrEP adherence. The application of a theory to understand PrEP adherence can help identify the active mechanisms underlying this behaviour within specific populations. A more comprehensive understanding of these variables can allow the development of tailored PrEP adherence interventions (Shrestha, Sansom, & Purcell, 2016).

The IMB model, describes behavioural and psychological determinants of HIV risk behaviours (Fisher & Fisher, 1992). This was then specifically adapted to explain antiretroviral adherence (Fisher et al, 2006). Informed by the Theory of Reasoned Action and the Theory of Planned Behaviour, the IMB model highlights three individual constructs; information, motivation and behavioural skills which are needed for an individual to engage in a health behaviour such as successful adherence (Deakin et al, 2005; Fisher et al, 2006). The IMB model of adherence behaviour defines 'information' as the perceived knowledge about medication use in that situation, whilst 'motivation' is described as both i) personal motivation (or treatment outcome expectancy and their perceived importance), and ii) social motivation, or the perception and importance of others' wishes in relation to adherence. Lastly, the behavioural skills construct is defined as the objective skills in taking medication as well as perceived self-efficacy in using those skills (Fisher et al, 2006). The model postulates that information and motivational constructs have direct effects on both behavioural skills and health behaviour. Behavioural skills is also hypothesised to directly impact health behaviour. As it describes motivational and behavioural skills which could change situationally, the IMB model is particularly well-suited to within-participant research. The model also incorporates moderating factors which are thought to affect adherence including; psychological health, living situation, access to medical care and substance use (Amico et al, 2009). A diagrammatical representation of the IMB model of ART adherence can be found below (Figure 2) (Fisher, Amico, Fisher, & Harman, 2008).

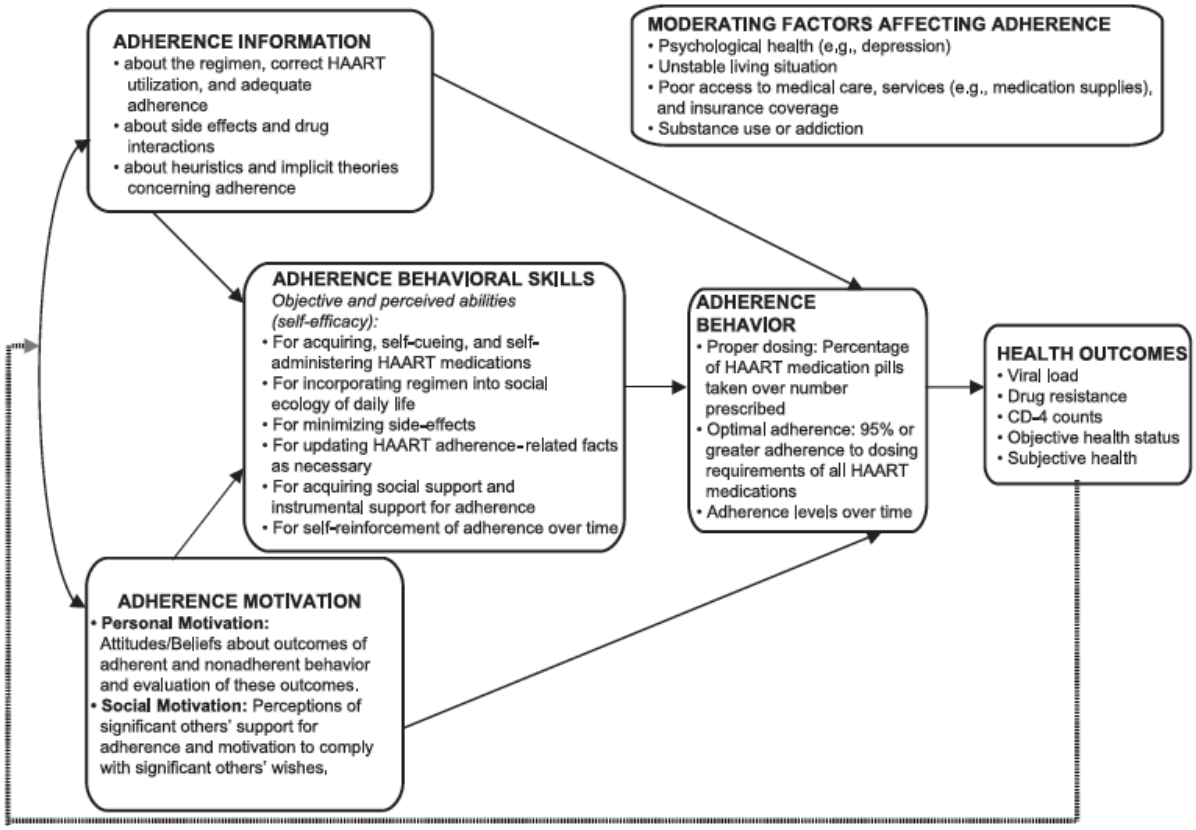


Figure 2: **The Information-Motivation-Behavioural Skills Model of ART Adherence (from Fisher, et al, 2006)**

The IMB model has been used frequently when exploring medication adherence in HIV positive samples (Amico et al, 2005; Horvath, Smolenski, & Amico, 2014; Starace et al, 2006). For example, Hawkins et al (2016) found non-adherence was not significantly associated with information or motivation but was significantly associated with behavioural skills. Non-adherence was also associated with variables not specified in the IMB model; lower positive affect and situational variables i.e. lack of routine, being out of the home and weekend days. Although, tentative a priori predictions can be made (i.e. that these behavioural/situationally specific variables would also be associated with PrEP adherence in high-risk HIV negative populations) researchers have suggested that the motivations to adhere to PrEP should not be

extrapolated from HIV positive samples as reasons are likely to differ (HIV negative populations are uniquely engaging in preventative medication strategies) (Tangmunkongvorakul et al., 2013).

At present, research has not concluded whether the IMB model is applicable in the context of PrEP adherence. The only related study was conducted by Shrestha et al (2016) who was the first study to empirically test and highlight the utility of the IMB model. Specifically, the study examined *willingness* to use PrEP (rather than actual use) amongst high risk HIV negative drug users in treatment. Consistent with Hawkins et al (2016), they found that there was no significant relationship between willingness to use PrEP and information or motivation but was mainly predicted by behavioural skills.

PrEP Access: Current UK context

In April 2017, Scotland became the first UK nation to approve NHS provision of PrEP to those at high risk of HIV transmission (Scottish Medicines Consortium, 2017). In the same month, NHS Wales committed to a three-year trial of PrEP to all high-risk populations (Welsh Government, 2017). Similarly, NHS England made £10 million available to Public Health England (PHE) to conduct the PrEP Impact clinical trial delivered through existing sexual health clinics. The PrEP Impact trial plan to enrol 10,000 participants over the next three years to address outstanding implementation questions for example, uptake and adherence within daily and event-based dosing regimens (NHS England, 2016). Alternatively, HIV negative MSM have two main routes to continue/initiate PrEP use: through a research trial or private prescription. The Gilead DISCOVER research trial, aims to compare Truvada (emtricitabine and

tenofovir disproxil fumarate, F/TDF) to Descovy (a new version of Truvada; a combination of emtricitabine and tenofovir alafenamide, F/TAF). This multi-national double-blinded RCT aims to test whether Descovy is as safe and effective as Truvada when used by MSM as a pre-exposure prophylaxis within a daily dosing regimen. Lastly, sexual health clinics at present offer clinical monitoring to patients who are using PrEP on private prescriptions, whether purchased on-line or from the clinic.

The proposed study

Overall, the literature above has highlighted that pharmacological interventions have a crucial behavioural component; adherence within the given population. As shown, the efficacy and need for HIV preventative methods does not guarantee their uptake and adherence. Thus, research must consider the social context in which these initiatives take place to ensure successful implementation (Dearing et al, 2013). Bridging the efficacy-effectiveness gap by understanding and optimising adherence is key to ensure funding and maximise public health impact (Baeten, Haberer, Liu & Sista, 2013). From the systematic review conducted it suggests that factors such as routine and planning and higher levels of actual risk behaviour could be between-participant predictors of PrEP adherence. However, it is not known if variation in these variables can explain inconsistent adherence observed within-individuals.

The current exploratory study aims to investigate within-participant situational differences in adherent and non-adherent episodes, informed by theory (the Information-Motivation-Behavioural Skills [IMB] model) in a cross-sectional study about retrospective adherence episodes. This aims to address the aforementioned

gap in the literature concerning determinants of adherent and non-adherent episodes in this population. No a priori predictions were made as previous research has not explicitly investigated the within-participant predictors of adherence within the PrEP-taking population. Previous researchers have suggested that the motivations to adhere to PrEP should not be extrapolated from other populations (e.g. HIV positive samples) as reasons are likely to differ (Tangmunkongvorakul et al, 2013).

The main research questions the study investigates are:

a) Which psychological factors (including those informed by the Information, Motivation, Behavioural Skills (IMB) Model), differentiate episodes of PrEP adherence versus PrEP non-adherence within participants?

b) Which behavioural factors (e.g. change in routine or day of the week) differentiate episodes of PrEP adherence versus PrEP non-adherence within participants?

Method

Design

A within-participants design was used.

Settings

Participants were recruited using convenience sampling from two London sexual health clinics (referred to as site 1 and site 2) who were both participating in the PrEP Impact and DISCOVER trials.

Inclusion criteria common to both Impact and DISCOVER trials were; MSM and transgender women (male at birth), HIV negative status and at high risk of HIV transmission. Inclusion criteria specific to the Impact trial were; transmen or heterosexuals; over the age of 16; willing to adhere to the recommended PrEP regimen (daily or event based) and re-attend the clinic every 3 months. Inclusion criteria specific to DISCOVER was; 18 years and older; have at least one of the following i) engaged in condomless anal intercourse with at least two male partners in the past 12 weeks (partners must be either HIV-infected or unknown HIV status), ii) history of syphilis or iii) rectal gonorrhoea or chlamydia in the past 24 weeks; adequate renal, liver and hematologic function. Impact is an open-label trial whereas DISCOVER is a blinded trial.

Sample

Participants

Participants had enrolled in the PrEP Impact or DISCOVER trials at either recruitment site or had attended one site for a general sexual health appointment or monitoring for a private PrEP prescription (either purchased online or in clinic). All recruited participants were approached between September and December 2017. The only reason given for not taking part when deemed eligible was insufficient time. The response rate was not able to be calculated. This was because the author was only referred potential participants whom were eligible and interested in taking part in the study. The number of times the study was discussed with eligible PrEP users who declined participation was not reported by the clinical team at either site.

Sample Size Calculation

Paired t-test analyses were used to inform an a-priori power calculation to estimate the required sample size. There have been no comparable within-participant studies which have examined PrEP adherence. Therefore, a study using similar methodology was chosen to calculate the effect size; Hawkins et al (2016) used a within-participant approach and applied the IMB model to explore antiretroviral medication adherence in young adults with perinatally-acquired HIV. The study found there was a small to medium effect size for difference in motivation to adhere between adherent and non-adherent episodes (d=0.38). There was a large effect size for the difference in behavioural skills between episodes (d=0.91). Therefore, to allow, both constructs to be examined together in the current study, the minimum number of participants required was 56 based on the smaller effect size.

Inclusion/ Exclusion Criteria

Inclusion criteria for the study was partly based on national eligibility for PrEP (NHS England, in press):

- HIV negative status
- Clinically assessed and deemed to be at high risk of HIV acquisition
- MSM or transgender women who have sex with men
- At least 16 years of age.

Other inclusion criteria included:

- Following a daily dosing regimen
- Prescribed and taking oral PrEP medication for at least three months.
- Must have shown inconsistent adherence in the previous month, that is, had one day when a dose was taken and one day when a dose wasn't taken within the last month
- Participants had to be under the care of an outpatient clinic where the research was conducted.
- Able to read English to understand and respond to questionnaire items.

The exclusion criteria were:

- Individuals deemed by the clinical team as not having the capacity to consent or to have emotional problems to a degree that might impact their ability to engage in the questionnaire.

Participants had to have taken PrEP for at least three months to ensure the study examined factors related to general PrEP adherence as opposed to habit formation. A non-adherent episode was determined by asking participants if they had one day in the last month where they did not take their PrEP medication. In context of a daily-dosing regimen the study used one missed dose as a marker for non-adherence. This definition was seen as way to maximise recruitment when compared to using the suggested level needed for PrEP effectiveness (four doses a week) as a marker for non-adherence (Grant, 2014). The period of one month was decided to balance the needs between using a shorter interval (to improve recall of the adherent/non-adherent episode) with a longer interval (to capture less frequent non-adherent episodes). Literature suggests that when collecting self-report medication adherence data an estimated adherence over 30 days may be the best time frame to balance the needs of shorter and longer intervals (Stirrat et al, 2015). Previous research has shown that self-reported antiretroviral adherence may be more accurate (i.e. less over-reporting) when one-month recall periods are used compared to three or seven-day periods (Lu et al, 2008). A recent PrEP implementation study (which measured adherence through biological and self-report methods) suggested that MSM can provide accurate self-report data over a 30-day period (Landovitz et al, 2017). Lastly, recall of a specific adherent/non-adherent episode may be more reliable and valid than estimates of behaviour over a longer period (Wilson, Carter & Berg, 2009).

Characteristics of the sample

Demographic information of the 67 recruited participants is presented in Table 8.

Table 8: *Demographic Information*

Variable		
Age	Mean (sd)	37.1 (10.2)
	Median (IQR, range)	35.4 (30-45, 18-62)
Occupational Status	Employed Full Time	57
	Employed Part Time	4
	Unemployed	0
	Student Full Time	1
	Student Part Time	1
	Retired	1
	Other	3
Highest educational qualification	GCSE/O-level	5
	A level/BTEC	11
	Degree level qualification	25
	Postgraduate qualification	26
Ethnicity	White	55
	Black	1
	Asian	3
	Mixed	4
	Other	4
Born in UK?	Yes	35
	No	32
Relationship status	Single	46
	Partner, living together	15
	Partner, living separately	6
Number of sexual partners (any type of sex) in the last month	Mean (median, IQR)	8.2 (3, 2-4)

Measures

Questionnaire Development

Detailed quantitative questionnaire data collection for both a specific adherent and non-adherent episode was obtained for each participant. There are no existing measures of psychological or situationally specific predictors of PrEP adherence. Therefore, to measure correlates of adherence a questionnaire was developed based on the IMB Skills Model questionnaire also known as the Life Windows Questionnaire measure (LW-IMB-AAQ) (Life Windows Project Team, 2006). The original 33-item scale questionnaire was developed for adults to measure adherence, specifically, IMB-related adherence barriers and facilitators (Appendix 7). Hawkins et al (2016), adapted this measure to explore situationally specific (episodic) medication adherence in young adults with perinatally-acquired HIV. This resulted in reducing the number of items to specifically focus on items that could vary situationally and a further reduction of items due to reliability analysis. The Life Windows measure includes nine information items which was reduced by Hawkins et al (2016) to three (adherent episode $\alpha = 0.98$; non-adherent episode $\alpha = 0.71$), ten motivation items which were reduced to seven (adherent episode $\alpha = 0.87$; non-adherent episode $\alpha = 0.85$) and fourteen behavioural items which were reduced to ten (adherent episode $\alpha = 0.71$; non-adherent episode $\alpha = 0.83$).

For the current study, the items used by Hawkins et al (2016) were adapted for the target group (PrEP users). This was done through consultation between the author and internal supervisor, reviewing the literature (e.g. Shrestha et al (2016) which was the first study to empirically test and highlight the utility of the IMB model within the PrEP population) and service user feedback (described below). For example, some

items were rephrased to be relevant to PrEP, “I knew how taking *the medication* could make me feel” was modified to “I knew how taking PrEP could make me feel”. Relevant behavioural and information items within the IMB subscales were added for example, type of sexual activity (behavioural) and perceived judgement from others regarding PrEP use (information) at the time/on the day of the episode. Items were also added to reflect the sexually active target population for example, participant’s beliefs about how PrEP would impact their enjoyment of sex. Lastly, a question asking the length of time since the adherent/non-adherent episode was added to gauge the potential impact of recall bias.

Service User Development

Service user feedback was used to assist questionnaire development. Service-users were sought by advertising on site 1’s social media page. Eight individuals contacted the author and were sent a copy of the draft questionnaire to give feedback in terms of the clarity, relevance, comprehensiveness and any other comments. This resulted in written feedback from eight individuals (2 HIV positive, 6 HIV negative) and led to adaptations to increase relevance for example, changing the names of street drugs, and formatting.

Final Questionnaire Items

The final questionnaire (prior reliability analysis) can be found in Appendix 10.

Background Data

At the beginning of the questionnaire background data were collected including descriptive demographic details (i.e. age, occupational status, education, ethnicity, country of birth, relationship status and living situation), number of sexual partners in the last month, length of time PrEP taken, how PrEP was obtained, whether the person had a daily routine for PrEP use, clinic attended for PrEP monitoring, number of times PrEP had been taken in the last seven days, whether the person experienced side effects and whether these were distressing.

Adherent and Non-adherent episodes

For each adherent or non-adherent episode, participants were asked to think about a time when they did or did not take their medication. Guided by the Cognitive Interview to facilitate memory recall, participants were asked to try to recall details about this day for example, where they were or how they felt. The Cognitive Interview refers to techniques used to enhance eyewitness memory (as opposed to cognitive interviewing, a technique used in scale development) (Fisher et al, 1987).

Situational Context

The following behavioural factors were assessed for each episode. Multiple questions were asked with a mixture of categorical and scale responses. These included:

- Day of the week
- How many days ago the episode was
- Whether another person or other prompts were there to remind them about the medication (yes/no)
- Routine (if usual day or routine different to normal due to planned or unplanned activity)
- Location (if at home; friend's house; partner's house; a public place such as work or college)
- Whether other people were present and, if so, who (alone; friend; partner; family; acquaintance; work colleague)
- If not alone, whether the other people present knew about the person taking PrEP (yes/no)
- Whether street drugs or alcohol were used around the time of medication (yes/no).
- How likely they thought sex was going to take place that day (5-point Likert scale; very unlikely, unlikely, neither likely or unlikely, likely or very likely)
- Whether they did have sex (yes/no)
- To what extent the individual felt they were at risk of HIV without taking PrEP (5-point Likert scale; very unlikely, unlikely, neither likely or unlikely, likely or very likely)

- If the individual did have sex that day; did they use a condom (yes/no), was it chemsex (yes/no), the HIV status of their sexual partner (negative/positive/don't know), sexual positioning/activity (anal insertive/anal receptive/oral sex/other) and whether the partner was a casual or regular partner.

In the non-adherent episode participants were asked two additional situational questions;

- Whether non-adherence was intentional or due to forgetting (I forgot/I chose not to take my medication).
- If the individual did have sex that day, they were asked if they used PEP medication (yes/no).

IMB Constructs and Reliability of Subscales

The IMB constructs were measured by scale questions rated on a 5-point Likert scale. Each item was introduced with “At the time I was due to take my PrEP” and presented as a statement. Responses included ‘very unlikely’, ‘unlikely’, ‘neither likely or unlikely’, ‘likely’ or ‘very likely’. This included 30 items in total (five items examined information, fourteen related to motivation and eleven items measured subjective behavioural skill). After the internal consistency for each subscale was assessed each subscale was refined to improve their psychometric properties. The five information items were reduced to three (adherent episode α = 0.79; non-adherent episode α = 0.77), the fourteen motivation items were reduced to thirteen (α = adherent episode α = 0.86; non-adherent episode α = 0.84) and the eleven behavioural items were reduced to ten (adherent episode α = 0.85; non-adherent episode α = 0.85). This suggests each subscale had either an acceptable or good level of reliability (Field, 2013).

Mood

Other situational variables included positive and negative affect at the time of each episode. The same items were used as those within The International Positive and Negative Affect Schedule Short Form (I-PANAS-SF) questionnaire (Thompson, 2007) shown to be reliable and valid within adult populations (Thompson, 2007). This scale has two five-item subscales (positive and negative affect) and uses a five-point Likert scale (*very slightly or not at all* to *extremely)*. The current study used the I-PANAS-SF to measure affect (adherent episode: positive affect α = 0.83, negative affect α = 0.83; non-adherent episode: positive affect α = 0.92, negative affect α = 0.85). These items were introduced with the sentence ‘How did you feel when it was time to take your PrEP?’.

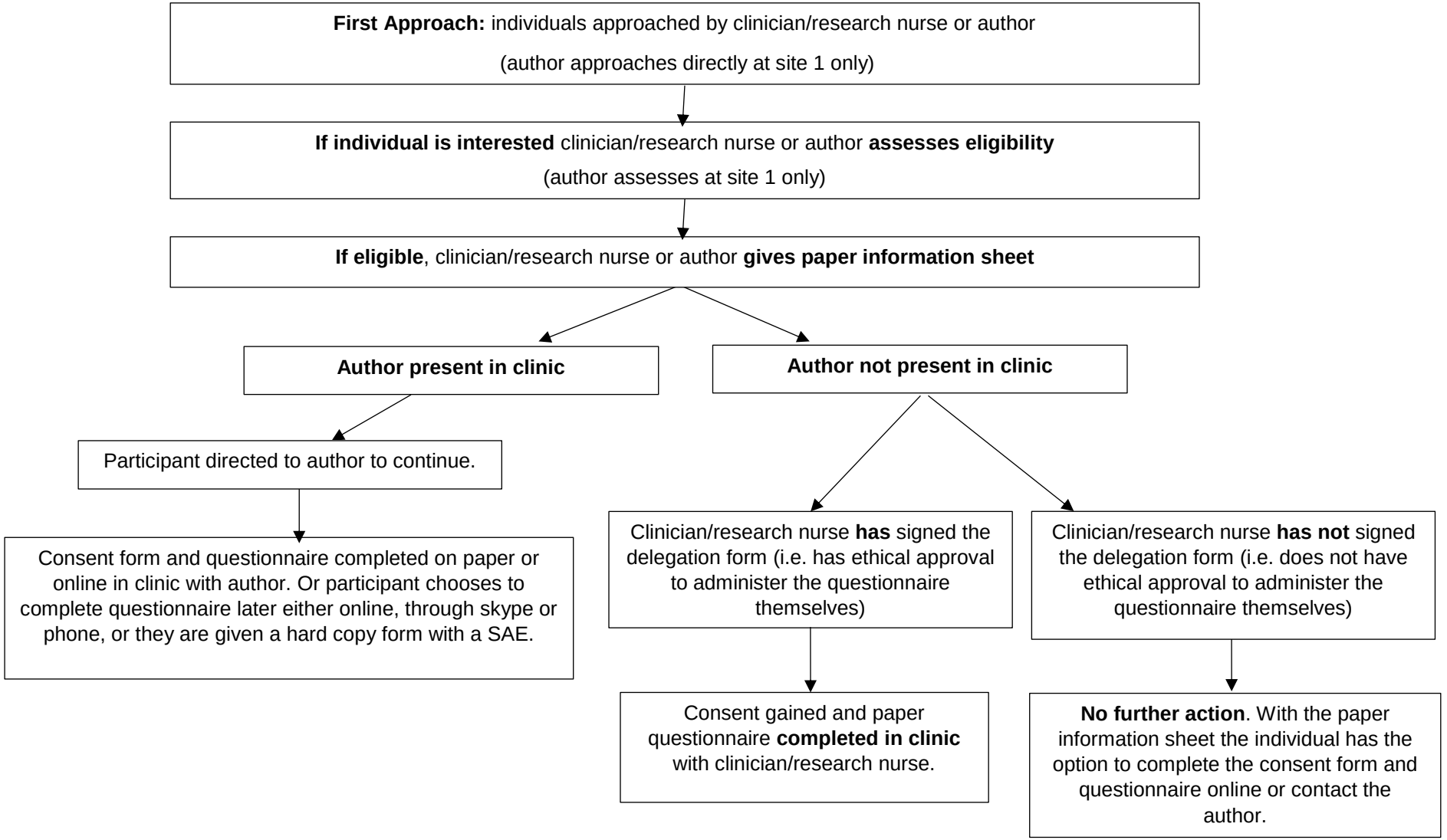
Study Procedure

A diagram of the study procedure can be found below (see Figure 3).

Potential participants were approached by their clinician, research nurse or by the author (author approached at site 1 only as approved by ethics) and told about the study. At site 1 clinic, the author approached all individuals whom had attended an Impact group consent meeting. The author also attended general sexual health clinics and monthly PrEP clinics where an allocated clinician told all individuals on their clinic list about the study and were signposted to the author. At recruitment site 2, all DISCOVER participants were approached by a research nurse. Across sites, eligibility was assessed by their clinician, research nurse or by the author (author assessed at site 1 only).

Eligible participants were given a paper information sheet which detailed further information about the study and researcher contact details. Interested and eligible individuals were then consented to participate by a research nurse (site 2 only) or the author. Participants had the option to complete the questionnaire on paper, online, through skype or telephone or were given a hard copy with a self-addressed envelope (SAE). Participants were allocated a unique study number linked to their date of birth to maintain confidentiality and anonymity of responses.

***Figure 3*: Study Procedure**



Ethics and Ethical Issues

The study was given NHS approval by the London-Surrey Borders Research Ethics Committee and approved by the Health Research Authority. The study gained ethical approval from the Royal Holloway University of London (RHUL) College Ethics Committee (for approval letters, see Appendices 1-4 and 6). Confirmation of Capacity and Capability was gained within each recruitment site NHS trust. The main ethical issues were gaining client consent, confidentiality and data storage which was covered in the Participant Information Sheet and consent forms (please see appendices 8-9).

A non-substantial amendment was made regarding the addition of an NHS recruitment site whose participation was confirmed post ethical approval. A substantial amendment was made so that members of the clinical team at recruitment sites could (once they had assessed eligibility) gain consent and administer the questionnaire themselves. Once approved, (please see appendix 5) all staff who agreed to do so, signed a delegation form in front of the principal investigator at each clinic as required. All staff on the delegation form had experience of gaining consent and administering questionnaires as part of their clinical role.

Analysis

Analysis was carried out in SPSS Statistics, version 21 (IBM Corp, 2012). Data was screened for normality and descriptive analysis were conducted; for normally distributed data, means were used and for non-normally distributed data, the median and inter-quartile range was used. The distributions of the difference scores for continuous variables were tested for skew and kurtosis to determine whether normality could be assumed and if parametric statistics could be used (Field, 2013).

Bivariate analysis

Bivariate comparisons were conducted between episodes of adherence and non-adherence. There were seven constructs within the analysis including; Information (1), Motivation (2) and Behavioural skills (3) (from the IMB model), affect (positive (4) and negative (5)), beliefs about the likelihood of sexual activity (6) and actual levels of sexual activity (7). An overall total score was calculated for each construct with multiple questions. Paired t-tests (for continuous variables that met assumptions for parametric statistics) or McNemar's chi-squared tests (for categorical variables, using Fisher's exact estimates for expected frequencies <5) were used to demonstrate possible differences on ratings of affect as well as situational, motivation and behavioural skills factors between adherent and non-adherent episodes. Uncorrected McNemar values were used (i.e. without Yates correction). This is recommended as a more conservative measure when conducting analysis of the independent 2x2 table (Fagerland, Lydersen, & Laake, 2013). If normality could not be assumed for continuous variables then paired t-tests with bootstrapping was planned. Effect sizes were calculated using Cramer's phi (ϕ) for categorical variables and Cohen's d for comparisons of means for continuous variables (Cohen, 1992). Conventions for Cohen's *d* are as follows: .20 – small effect;

.50 – medium effect; .80 – large effect) and Cramer's phi values for 2x2 contingency tables indicate effect sizes as follows: .10 – small; .30 – medium; .50 – large (Cohen, 1992). The exploratory nature of the current research has implications for multiplicity corrections (i.e. the use of Bonferroni corrections) needed to control for the increased likelihood of Type I error in this study design (Bender & Lange, 2001). However, the current study was not conducting multiple exploratory analyses on the same constructs (e.g. one paired t-test was conducted for whether location differentiated adherent and non-adherent episodes) therefore, Bonerroni corrections were not conducted.

Multivariate analysis

Conditional logistic regression analysis investigated whether more than one independent variable in combination predicted the dependent variable as well as to investigate independent relationships with adherence. Variables were included dependent on their significance in the bivariate analysis (defined as a p-value >0.05) and relevance to the IMB model.

Results

Sixty-seven participants completed a paper version of the questionnaire during their clinic appointment (i.e. no-one completed the questionnaire online or via skype), Table 9, below, presents the descriptive PrEP-related information of the sample. Due to small cell sizes for some categories, some variables are grouped.

Table 9: ***Descriptive PrEP-related information***

Variable		N(%)	Grouped Categories
Length of time PrEP taken	3-4 months	18 (27)	
	5-8 months	13 (19)	
	9-12 months	10 (15)	
	1 year+	26 (39)	
How PrEP obtained	Online	44 (66)	*Online* *44*
	Research/Study Participant	14 (21)	*Research/Study Participant* *14*
	Private Prescription	7 (10)	*Other*
	Friend	2 (3)	*9*
Daily routine for PrEP	Yes	60 (90)	
	No	5 (7)	
	Missing	2 (3)	
Clinic attended for PrEP monitoring	Site 1	61 (91)	
	Site 2	6 (9)	
How many times PrEP taken in the last 7 days	0	4 (6)	*0 doses: 4*
	1	1 (2)	*1-3 doses*
	2	1 (2)	*2*
	3	0	
	4	3 (4)	*4-6 doses*
	5	1 (2)	*19*
	6	15 (23)	
	7	40 (61)	*7 doses: 40*
Current experience of side effects	Yes	7 (10)	
	No	60 (90)	

Categorical Variables: Data exploration and grouping

Table 10 below, presents the frequencies of responses for non-adherent and adherent episodes for categorical variables. Due to small cell sizes for some categories some variables were grouped. The mean number of days prior to the adherent episode was 2.6 days (SD= 3.05) and 11.9 days (SD= 10.06) for the non-adherent episode.

Table 10: ***Categorical variables between adherent and non-adherent episodes (n=67)***

Variable		**Adherent episode (frequencies)**		**Non-adherent episode (frequencies)**	
Use of Reminders	Yes	27		19	
	No	39		47	
	Missing	*1*		*1*	
Weekday	Monday	14	*Mon-Fri*	3	*Mon-Fri*
	Tuesday	5	*55*	10	*43*
	Wednesday	10		13	
	Thursday	16		12	
	Friday	10		4	
	Saturday	3	*Sat-Sun*	9	*Sat-Sun*
	Sunday	4	*7*	11	*20*
	Missing	*5*		*4*	

Variable		Adherent episode (frequencies)		Non-adherent episode (frequencies)	
Normality of Day	Normal	62	*Normal 62*	41	*Normal 41*
	Not normal: unexpected	3	*Not normal 5*	10	*Not normal 26*
	Not normal: planned	2		12	
	Other	0		4	
Location	Own home	59	*Own home 15*	42	*Own home 42*
	Partner's home	1	*Somewhere Else 8*	0	*Somewhere Else 25*
	Friend's home	0		6	
	Public place	5		7	
	Somewhere else	2		12	
Who with at time of dose/missed dose	Alone	53	*Alone 53*	42	*Alone 42*
	Friend	2	*Not alone 14*	7	*Not alone 25*
	Partner	7		6	
	Family	2		3	
	Acquaintance	0		1	
	Work colleague	2		5	
	Someone else	1		3	
Did person know about PrEP use?	Yes	13		19	
	No	1		6	
	Not Applicable	56		44	
Substance use	Yes	6		14	
	No	59		51	
	Missing	*2*		*2*	

Variable		Adherent episode (frequencies)	Non-adherent episode (frequencies)
Sex (any type) that day	Yes	21	15
	No	46	52
Did sexual partner know about PrEP use?	Yes	13	11
	No	8	4
	Not Applicable	46	52
Use of condom	Yes	1	0
	No	20	15
	Not Applicable	46	52
Chemsex	Yes	3	5
	No	18	10
	Not Applicable	46	52
HIV status of sexual partner	HIV negative	7	7
	HIV positive	5	3
	Not known	9	5
	Not applicable	42	56
Type of sex: Top	Yes	13	12
	No	8	3
	Not Applicable	46	52
Type of sex: Bottom	Yes	13	8
	No	8	7
	Not Applicable	46	52
Type of sex: Oral	Yes	16	8
	No	5	7
	Not Applicable	46	52
Type of sex: Other	Yes	0	1
	No	21	14
	Not Applicable	46	52

Variable		Adherent episode (frequencies)	Non-adherent episode (frequencies)
Casual or regular partner	Casual	13	12
	Regular	8	3
	Not Applicable	46	52
Use of PEP	Yes		2
	No		13
	Not Applicable		52

Continuous variables: Data screening and descriptive statistics

Descriptive statistics for psychological variables and somatic symptoms for both episodes are presented in Table 11 below.

Table 11: ***Within-participant descriptive data for psychological variables and somatic symptoms per episode***

Variable (minimum-maximum score)	Episode	Median (IQR)	Mean	SD
Information (3-15)	Adherent	15 (14-15)	14.36	1.14
	Non-adherent	15 (13-15)	14.09	1.38
Motivation (13-65)	Adherent	54 (47-61)	53.75	7.6
	Non-adherent	54 (48-61)	54.1	8.05
Behavioural Skills (10-50)	Adherent	44 (40-49)	44.16	4.97
	Non-adherent	42.5 (38.25-48)	42.39	6.17
Positive Affect (5-25)	Adherent	16 (12-20)	15.82	5.47
	Non-adherent	14 (9-19.5)	14.42	6.27
Negative Affect (5-25)	Adherent	5 (5-6)	6.14	2.51
	Non-adherent	5 (5-7)	6.4	2.53
Somatic symptoms "I didn't feel ill" (1-5)	Adherent	5 (4-5)	4.57	0.66
	Non-adherent	5 (4-5)	4.38	0.97

Exploratory bivariate analysis:

Relationships between behavioural situational factors and adherence

Day of the week

Participants were more likely to adhere on a weekday and not on the weekend, compared to the reverse pattern. The difference in this pattern was significant with a medium effect size (χ^2=6.37, p=.01; ϕ= .33)

Table 12: ***Frequencies for "Day of the week"***

		Non-adherent episode		
		Weekday	**Weekend**	**Total**
Adherent episode	**Weekday**	38	15	53
	Weekend	4	3	7
	Total	42	18	60

Use of Reminders

Eleven people reported having used reminders to prompt them to take their medication at the time of adherent episode and not at the time of non-adherent episode, only three people reported the opposite pattern. The difference in this pattern was significant with a small to medium effect size (χ^2=4.57, p=.03; ϕ =.26).

Table 13: ***Frequencies for "Use of Reminders"***

		Non-adherent episode		
		Used reminders	**No reminders**	**Total**
Adherent episode	**Used reminders**	16	11	27
	No reminders	3	36	39
	Total	19	47	66

Normality of the day

Twenty-five people reported an adherent episode on a normal day and a non-adherent episode on a day that was not normal, only four people reported the opposite pattern. The difference in this pattern was significant with a medium to large effect size, (χ^2=15.2, p= <.001; ϕ =.48).

Table 142***: Frequencies for "Normality of the day"***

		Non-adherent episode		
		Day was normal	**Day was not normal**	**Total**
Adherent episode	**Day was normal**	37	25	62
	Day was not normal	4	1	5
	Total	41	26	67

Location

Two people reported being somewhere else at the time of the adherent episode and at home at the time of non-adherent episode; nineteen people reported the opposite pattern. The difference between these was significant with a medium to large effect size, (χ^2=13.76, p= <.001; ϕ =.45).

Table 15: ***Frequencies for "Location"***

		Non-adherent episode		
		Own Home	**Somewhere Else**	**Total**
Adherent episode	**Own Home**	40	19	59
	Somewhere Else	2	6	8
	Total	42	25	67

Who with at time of dose/missed dose

Five people reported being with someone else at the time of the adherent episode and alone at the time of non-adherent episode; sixteen people reported the opposite pattern. The difference between these was significant, representing a small to medium effect size (χ^2=5.76, p=0.02, ϕ = .29).

Table 16: ***Frequencies for "Who with at time of dose/missed dose"***

		Non-adherent episode		
		Alone	**With someone**	**Total**
Adherent episode	**Alone**	37	16	53
	With someone	5	9	14
	Total	42	25	67

Substance Use

Ten people reported that were not using substances (alcohol or drugs) at the time of the adherent episode and were at the time of non-adherent episode; two people reported the opposite pattern. The difference, between these was significant, representing a small to medium effect size (χ^2=5.33, p=0.02, ϕ =.29).

Table 17: ***Frequencies for "Substance Use"***

		Non-adherent episode		
		Yes	**No**	**Total**
Adherent episode	**Yes**	4	2	6
	No	10	49	59
	Total	14	51	65

Sex that Day

Fourteen people reported having sex on the day of the adherent episode and not on the day of the non-adherent episode; eight people reported the opposite pattern. The difference between these was not significant, representing a small effect size (χ^2=1.64, p= 0.20, ϕ = .16).

Table 18: ***Frequencies for "Sex that day"***

		Non-adherent episode		
		Yes	**No**	**Total**
Adherent episode	**Yes**	7	14	21
	No	8	38	46
	Total	15	52	67

Somatic Symptoms

Bivariate comparisons between episode on the measures of somatic experience were carried out using bootstrapped paired t-tests as the difference score was not normally distributed. There was no significant difference in reports of "I felt ill" between episodes .18, 95% BCa CI [0, .38], (t(62)= 1.59, p =0.13).

Theory-driven Bivariate Analysis

Information

On average, participants scored higher on the information subscale during the adherent episode (mean= 14.37, SE= 0.14) than the non-adherent episode (mean= 14.10, SE= 0.18). This difference, 0.27, 95% BCa CI [0.05, 0.51], was significant between episodes: participants rated their perceived knowledge about medication use more highly at the time of taking their medication than when they missed their medication $t(62) = 2.21$, $p = 0.04$, representing a small-sized effect $d = .28$.

Motivation

On average, participants scored lower on the motivation subscale during the adherent episode (mean= 53.51, SE = .95) than the non-adherent episode (mean= 54.1, SE= 1.01). This difference, -.59, 95% CI [-1.56, 0.38], was not significant ($t(62) = -1.21$, $p = 0.23$, $d = 0.15$).

Behavioural Skills

On average, participants rated their behavioural skills in taking PrEP higher at the time of the adherent episode (mean= 43.98, SE= 0.62) than at the time of the non-adherent episode (mean= 42.39, SE= 0.77). This difference, 1.59, 95% CI [0.68, 2.5], was significant $t(63) = 3.5$, $p = <.001$, representing close to a medium-sized effect $d = 0.44$.

Affect

On average, participants scored higher on the positive affect subscale during the adherent episode (mean= 16.10, SE= 0.67) than the non-adherent episode (mean= 14.37, SE= 0.78). This difference, 1.73, 95% BCa CI [0.76, 2.73], in positive affect was significant between episodes: t(62) = 3.21, p = 0.002, representing close to a medium sized effect d= .41.

On average, participants scored lower on the negative affect subscale during the adherent episode (mean= 6.15, SE= 0.31) than the non-adherent episode (mean= 6.4, SE= 0.31). This difference, -.25, 95% CI [-.76, .27], was not significant (t(64) = -.95, p = 0.35, d= 0.12).

Theory-Driven Exploratory Multivariate Analysis

Multivariate analysis was conducted to investigate the combined and independent contribution of the significant IMB predictors (information and behavioural skills) of non-adherent episodes. The IMB model also includes mental health alongside the central IMB variables. As there was a significant bivariate relationship between positive affect (conceptually related to mental health) and adherence, positive affect was added as an independent variable in the multivariate analysis. The outcome variable was dichotomous (adherent or non-adherent episode) and repeated, therefore a conditional logistic regression (CLR) model was used (Tabachnik & Fidel, 2006).

Correlations between behavioural skills, information and positive affect were investigated as an initial test for potential mulitcollinearity problems. To be problematic in CLR, correlation coefficients would need to be greater than 0.70 (Chatterjee & Hadi, 2015). Behavioural skills and positive affect were significantly correlated for both adherent (r=.255, p= .04) and non-adherent (r=.449, p= <.001) episodes. There was no correlation between information and positive affect for either adherent (r=.17, p=.18) or non-adherent (r=.241, p=.05) episodes. Behavioural skills and information were significantly correlated for both adherent (r=.541, p= <.001) and non-adherent (r=.604, p= <.001) episodes. These statistics suggested there may not be a multicollinearity issue with these variables.

CLR model

The CLR assumptions were tested for this model (Table 19): VIF and tolerance values were both close to 1; Pearson's standard residuals demonstrated no values higher than 3; DfBeta measure of leverage were not above 1, therefore no assumptions were violated.

Table 19*: CLR Model with information, behavioural skills and positive affect*

	B	Std. Err.	Sig.	Exp(B)	95% Confidence Interval	
Information	-.76	.449	.09	.47	.20	1.13
Behavioural Skills	-.30	.132	.02	.74	.57	.96
Positive affect	-.15	.097	.13	.86	.71	1.05

An overall model including information, behavioural skills and positive affect was significantly predictive of adherent episode ($\chi^2(3)= 14.723$, p=.002). After controlling for shared variance between information, behavioural skills and positive affect, there was not an independent relationship between information and non-adherent episode (AOR=0.47, 95%CI 0.20-1.13, p=0.09) or positive affect and non-adherent episode (AOR= 0.86, 95%CI 0.71-1.05, p=0.13). There was an independent relationship between behavioural skills and non-adherent episode (AOR=0.74, 95%CI 0.57-0.96, p=0.02) with lower behavioural skills scores associated with non-adherence.

Discussion

Overview of study findings

This study aimed to explore the situational psychological and behavioural factors which differentiate episodic PrEP adherence and non-adherence amongst MSM at high-risk of HIV acquisition. Lower reported information (small effect size), behavioural skills (small to medium effect size) and lower positive affect (close to a medium effect size) were associated with non-adherent episodes in bivariate analysis. Multivariate analysis including information, behavioural skills and positive affect was significantly predictive of non-adherent episodes, although only behavioural skills was statistically significant independently. Negative affect or motivation was not related to non-adherence in bivariate analysis. Multiple behavioural factors were associated with PrEP non-adherence; non-normality of the day, being out of the home (close to large effect sizes), weekend days (medium effect size), lack of reminders, not being alone and substance use (close to medium effect sizes).

Behavioural skills

The finding that adherence was related to higher levels of behavioural skills is consistent with the IMB model which theorises a direct pathway from PrEP-related behavioural skills and adherence behaviour. Behavioural skills in the IMB model includes the objective and perceived abilities (i.e. self-efficacy) to self-cue and self-administer PrEP, incorporate PrEP into everyday life and cope with side-effects (Fisher et al, 2006). The current finding is consistent with IMB's theoretical notion that behavioural skills are the most proximal factor and critical prerequisite to adherence behaviour (Fisher, Amico, Fisher & Harman, 2008). This result was also consistent with the findings from Shrestha et al (2016) conducted earlier in the PrEP cascade

which showed that willingness to use PrEP was mainly predicted by behavioural skills. Behavioural skill has shown to be related to ART medication adherence cross-culturally in HIV positive populations (Amico et al, 2005; Horvath, Smolenski, & Amico, 2014; Starace et al, 2006). The current finding also suggests that behavioural skills differ situationally. This is consistent with findings using a similar within-participant methodology, with young adults with perinatally-acquired HIV and adults with Beta-Thalassaemia-Major (i.e. that adherence was related to higher levels of behavioural skills) (Hawkins et al, 2016; Vosper et al, in press). Bandura (1986) theorised that in situations with increased challenges to achieve a behaviour (e.g. adherence), increased self-efficacy helps to promote an individuals' efforts and persistence to problem solve. Increased behavioural skills (inlcuding self-efficacy) therefore could have helped promote adherence when participants faced situational challenges

Information and Motivation

Adherence was related to higher levels of information in bivariate analysis but this did not retain significance in multivariate analysis. Adherence was not associated with other key constructs (motivation) in the IMB model. This is inconsistent with the IMB model that posits adherence-related information and motivation are associated with adherence-related behavioural skills and are key components necessary for adherence (Fisher et al, 2006). However, the current finding is consistent with Shrestha et al (2016) whom found that willingness to use PrEP was not predicted by information or motivation. It is also consistent with findings where the IMB model has been applied to ART adherence (Amico et al, 2009; Horvath, Smolenski, & Amico, 2014; Santillán et al, 2015; Starace et al, 2006). Furthermore, studies using a similar within-participant methodology, found no relationship between information and

motivation and ART adherence (Hawkins et al, 2013) and no relationship between motivation and chelation adherence (i.e. treatment for Beta-Thalassaemia-Major) (Vosper et al, in press). This finding might suggest that information and motivation may not be sufficient for PrEP adherence. These components may not have a direct impact on adherence behaviour when adherence requires multiple behavioural skills.

Information and motivation may not differ situationally and both constructs been shown inconsistent relationships with other HIV-related health behaviours (e.g. protected anal intercourse) amongst high risk MSM (Kalichman, Picciano, & Roffman, 2008). Additionally, the review highlighted two studies which reported inconsistent findings regarding the relationship between PrEP knowledge and adherence (Liu et al, 2014; Liu et al, 2016). In the current study, the information construct was only measured by three items. The lack of differences in scores which meant information did not maintain significance in multivariate analysis may have been due to ceiling effects. Due to the small sample size and dangers of overfitting (Babyak, 2004) results from the CLR model should be interpreted with caution. The information construct had high standard errors and confidence intervals, this could mean that findings were imprecise and resulted in a type II error. This would require replication in a larger sample to investigate these effects further. It is possible that motivation differs *between* people but not *within* people. Alternatively, the lack of differences in motivation scores may have been due to demand characteristics influenced by the context of PrEP access; participants may have felt the need to express their motivation to use PrEP even in non-adherent episodes to support PrEP access. The review highlighted that MSM PrEP users can feel a social motivation for their PrEP use (i.e. a sense that participation and adherence could benefit their social group) (Gilmore et al, 2013;

Tangmunkongvorakul et al, 2013). Also, given that PrEP access is relatively novel, the sample mainly consists of 'early adopters' whom may be highly motivated for PrEP use, as reflected in the motivation scores. Additionally, the majority (66%) of non-adherent episodes were reported to be due to forgetting as opposed to intentional non-adherence which may explain the lack of differences in motivation between episodes. Lastly, the lack of differences in scores for both constructs may be due to the non-validated scale used in the current study. Despite good reliability, the measurement of these constructs may have been imprecise and resulted in a type II error. For example, it may difficult to recall or endorse specific beliefs experienced at the time of the episode.

Affect

Non-adherence was associated with lower positive affect in bivariate analyses and had no association with negative affect. This is inconsistent with the theoretical IMB model which predicts that mental health moderates the central IMB variables. However, this finding is consistent with Hawkins et al's (2016) within-participant study which also found lower positive affect was associated with non-adherence to ART amongst HIV-positive young adults. An RCT found that a patient education intervention enhanced with a positive-affect induction and self-affirmation led to significantly higher medication adherence compared to patient education alone in hypertensive African Americans (Ogedegbe et al, 2012). Positive affect and self-affirmation have shown to influence the acceptance of health messages and adoption of positive health behaviours (Armitage et al, 2008). This finding is also consistent with Van Cappellen et al (2017) whom theorise an 'upward spiral' framework whereby positive affect contributes to recursive processes that support health behaviours (i.e. positive affect makes behaviours more likely and behaviours reinforced by positive

affect are more likely to be maintained). This has been supported by research using an ecological momentary assessment (EMA) methodology which found situational variations in positive affect were predictive of engagement in exercise (Emerson, Dunsiger & Williams 2017). One criticism of the I-PANAS-SF used is that it only measures one dimension of positive affect. This measure has been critiqued for only measuring 'activated' positive affect (e.g. enthusiastic and inspired) as opposed also incorporating 'non-activated' positive affect (e.g. content and satisfied) (Peterson et al, 2013). This could have influenced positive affect scores (i.e. caused a reduction of differences in scores) which meant it did not maintain significance in multivariate analysis. Alternatively, positive affect also had relatively high standard errors and confidence intervals which could mean that findings were imprecise and resulted in a type II error. This may why explain positive affect did not retain significance in multivariate analysis and would require replication in a larger sample to investigate potential effects further. In relation to negative affect, this finding was inconsistent with studies that found depressive scores were associated with PrEP non-adherence amongst transgender women (TGW) who have sex with men (Mehrotra et al, 2015) and affective factors including depression acting as barriers to ART adherence (Uthman et al 2014). Results may be representative of the MSM PrEP-using population as they are not a depressed sample. Alternatively, a floor effect may have occurred as participant negative affect scores were clustered at the minimum possible score which could have resulted in a type II error (Martin, Bateson & Bateson, 1993).

Behavioural situational variables

Several situational behavioural variables were also related to non-adherence. This finding is consistent with within-participant research findings that non-adherence was associated with situational behavioural variables not included in the IMB model; lack of routine, being out of the home and weekend days (Hawkins et al, 2016; Vosper et al, 2013). It is also consistent with the current review findings that having an established routine and use of reminders facilitated adherence whilst frequent travel, not being at home and busy lifestyles acted as a barrier to PrEP adherence (Gilmore et al, 2013; Hosek et al, 2013; Mugo et al, 2015; Storholm et al, 2017; Tangmunkongvorakul et al, 2013). Furthermore, it is consistent with studies with HIV-positive individuals which found lifestyle factors (e.g. changes to daily routine or being away from home) can negatively influence ART adherence (Shubber et al, 2016). The current findings could be indicative that non-adherence is more likely when an individual's usual routine is disrupted. When out of the home MSM may not have access to PrEP and/or lack access to usual memory cues to take their medication (i.e., it's more difficult to plan and act on the intention to adhere). This disruption in routine may be most likely at the weekend and/or when substances are used. Of interest, most studies examined in the review found no relationship between substance use and PrEP adherence (Grant et al, 2014; Landovitz et al, 2017; Liu et al, 2014; Liu et al, 2016; Mugo et al, 2015). However, comparisons between current and review findings are limited as the current study used a sub-set of the PrEP taking population (i.e. MSM with inconsistent adherence) whereas those in the review used a between-participant design and included all PrEP users. MSM may be less likely to take PrEP when others are present due to fear of stigmatisation as highlighted in PrEP studies examined in the review (e.g. anticipated fear the individual will be perceived as

sexually promiscuous) (Arnold et al, 2017; Gilmore et al, 2013; Tangmunkongvorakul et al, 2013). Of interest, during 19 out of 25 non-adherent episodes and 13 out of 14 adherent episodes where the PrEP user was not alone, the other person was aware of PrEP use (i.e., it suggests that non-adherence in the presence of someone not aware of the PrEP use is more common that adherence in the presence of someone not aware of the PrEP use). This may suggest that disclosure of PrEP use to others alone may not necessarily make it easier to take PrEP medication if their routine is disrupted (e.g. they are away from home) which may affect PrEP adherence. Overall, differences in behavioural factors between adherent and non-adherent episodes suggests that lifestyle factors which may vary over time and contexts may influence PrEP adherence. Sex on the day of the episode was not associated with adherence. This was consistent with the review which found that most studies found no relationship between MSM PrEP adherence and sexual behaviour (Landovitz et al, 2017; Liu et al, 2014; Mugo et al, 2015; Sagaon-Teyssier et al, 2016; Tangmunkongvorakul et al, 2016). Future research could investigate numerous adherent and non-adherent episodes using daily diaries/EMA over a period of time to gain a more representative picture of the predictors (including sex) related to PrEP adherence.

Limitations

There are no validated situational measures available to measure adherence cognitions. The validity and reliability of the measurement instrument developed in the current study should be interpreted with caution. For example, participants were asked about retrospective cognitions which could have been susceptible to recall bias. However, the items designed to measure the IMB constructs had acceptable to good levels of internal reliability for each episode. The overall measure was developed in consultation with service-users from the MSM population to explore the clarity, relevance and comprehensiveness of the items. The IMB constructs within the questionnaire were all highly correlated (not reported in the results section) which is in line with the theoretical model. This suggests that IMB items used in the questionnaire were measuring IMB constructs. Also, there were different relationships between each construct and adherence, which might support the validity of the measure.

The participants were recruited from two London sexual health clinics. This may suggest that the current findings may have limited generalizability to other geographical areas or people with similar access to health-care services. The sample were highly educated, mainly actively sought PrEP through online methods and had high levels of self-reported adequate adherence observed (i.e. 91% achieved 4 or more doses in the previous week). This suggests that participants may have been a highly motivated sample. Furthermore, the sample were a sub-set of the PrEP taking population (i.e. those who showed inconsistent adherence rather than all PrEP users) and may not be representative of the wider MSM population, limiting the generalisability of findings. This means that the predictors of PrEP adherence identified in the current study may differ in the wider MSM population. Therefore, when

delivering adherence interventions although current findings give clinicians some direction about what they could focus on predictors would have to be tailored to the individual. However, when compared to the UK PROUD RCT study the MSM baseline characteristics were similar to the current sample. For example, the median age of participants for both studies was 35 years, similar numbers were born outside of the UK (PROUD 40%, current sample 47%), the majority of participants were university graduates (PROUD 61%, current sample 76%) and a minority of participants were living with their partner (PROUD 30%, current sample 22%).

Another limitation was that the study had no objective measure of adherence and relied upon retrospective self-report of cognitions and emotions. When giving ratings participants already knew that they had not adhered and responses may have suffered from retrospective bias or difficulties remembering the specific episodes. However, the questionnaire presented behavioural situational questions at the beginning to orient participants to the specific episode and used elements of the Day Reconstruction Method (Kahneman et al, 2004) to facilitate accurate recall of episodes. Furthermore, asking participants about episodes only in the last 30 days may have limited erroneous recall. Most participants described recent episodes which occurred an average of three (adherent) and twelve (non-adherent) days ago, which may have limited the impact of forgetting.

Another criticism was that the questionnaire asked participants about one taken and missed PrEP dose which may not be representative of PrEP adherence episodes. Additionally, 66% of non-adherent episodes were reported to be due to forgetting as opposed to intentional non-adherence. There may be different predictors between intentional and non-intentional (i.e. forgetting) non-adherence. Previous research has

shown that there were different predictors associated with intentional and unintentional non-adherence to ART medication in an adult HIV positive sample (Wroe & Thomas, 2003). This was not explored in the current study due to not having a large enough sample size and could be investigated in future research. An oversight of the questionnaire used was that adherent/non-adherent episodes were not counterbalanced. This could have introduced order-effects which could have influenced study results (Gravetter & Forzano, 2018).

Research Implications

There may be different predictors of PrEP use between individuals who achieved adequate levels of PrEP protection (i.e. four or more doses of PrEP a week) with individuals who did not. Future research with larger samples would allow the comparison of predictors between non-clinically significant and clinically significant missed PrEP doses. Larger samples would also allow the comparison of predictors of intentionally and unintentionally missed doses. Future research needs to continue to examine PrEP adherence amongst diverse populations (e.g. TGW) and MSM subpopulations (e.g. Black, Asian and minority ethnic [BAME] MSM) to increase the generalisability of findings and delineate specific facilitators/barriers to PrEP use. It would also be pertinent to continue to examine the predictors related to PrEP use within diverse implementation settings, (i.e. predictors of PrEP adherence amongst MSM who have PrEP freely accessible compared to those who self-fund their PrEP) across multiple episodes of adherence/non-adherence as well as within different PrEP regimens (i.e. event-based dosing).

Prospective studies, using EMA of adherence episodes (e.g. using smart-app technology to ask individuals questions about episodes through daily text), would reduce the reliance upon retrospective memory and could enhance measurement reliability and validity (Runyan et al, 2013; Shiffman et al, 2008). Future research could explore the feasibility and validity of using this method by comparing this with retrospective self-report. This would also allow more than one episode to be measured and may give more representative picture of PrEP adherence. Additionally, an experimental study randomising MSM PrEP users to either a behavioural skills intervention or treatment as usual could help to establish causation. Findings give support to some aspects of the IMB model to help explain PrEP adherence, however, also highlight predictors related to PrEP adherence which are not acknowledged within the model (i.e. situational behavioural factors such as location or positive affect). Future research should incorporate but not be limited to this theoretical model when deciding which predictors to investigate in relation to PrEP adherence.

Practice Implications

The findings suggest that across situations people may need different PrEP information or behavioural skills to adhere. For example, if outside of their own home, it may be particularly important to self-cue the administration of their PrEP medication. Alternatively, in a situation where alcohol is present, an individual may require the information regarding PrEP's interactive effects with alcohol (whereas in other situations this may not be relevant). The findings suggest that modifiable situational psychological and behavioural factors are important for PrEP adherence. Clinically, this suggests that assessments of facilitators and barriers of PrEP adherence could focus upon situational variations in information, positive affect, behavioural skills and behavioural factors (e.g. location, day of the week). The barriers highlighted could then be used within a problem-solving based therapy to conceptualise high-risk situations for non-adherence and alternative strategies could be co-constructed to facilitate adherence in these situations. Advanced planning may take the form of implementation intentions (i.e. whereby an individual would plan when and how they to enact PrEP adherence in specific situations). Observational studies have shown a relationship between these interventions and behaviour (Gollwitzer & Sheeran, 2006). In relation to existing PrEP adherence programmes, current findings could help by giving conversations a specific focus (e.g. asking about a client's time spent outside of the home). Only one intervention (i.e. 'Next Step Counselling' (NSC), a problem-solving therapy) outlines specific barriers and facilitators to discuss with clients. The current findings support the categories used in NSC assessment forms (i.e. asking clients regarding their substance use, disruption in routine and use of reminders) (Amico et al, 2012). This intervention could be supplemented by the addition of the current findings (e.g. asking clients about their positive affect, weekends and days

when they are not alone). Findings also support the use of technological (e.g. two-way texts) and physical (e.g. pill boxes) methods as reminders used by one intervention to facilitate PrEP adherence (Liu et al, 2014). Current findings support WHO guidelines (2017) that within PrEP assessment and adherence counselling sessions clinicians could support adherence by increasing individuals' information about their medication use (i.e. what to do when forgetting medication, side effects and interactive effects with other substances/medications) and behavioural skills (e.g. how to incorporate PrEP into their daily routine, acquiring social support and use of reminders). The current findings also highlight that affect and other behavioural factors may be important for PrEP adherence and therefore interventions should consider focusing upon an individual's mood (specifically positive affect) and certain situations such as the weekend, when out of the home or when an individual's day is not normal. Lastly, WHO guidelines (2017) recommend but give no specific guidance regarding how differentiated care should be implemented within healthcare settings. The current study findings could be used to identify when an individual may be at most at risk of non-adherence (e.g. when they report they are regularly out of the home, have low behavioural skills or low positive affect) and who may benefit from additional clinical support at that time (i.e. adherence interventions).

Integration, impact and dissemination plan

Integration

The systematic review provided a clear rationale and assisted the development of the empirical article. The literature within the review highlighted the problem, that is, the issue of PrEP non-adherence amongst MSM and its critical role in effective PrEP implementation to reduce HIV acquisition. This provided a clear rationale for the systematic review and empirical article which both focused on the issue of PrEP adherence within the MSM population. Specifically, both pieces aimed to examine the predictors of PrEP adherence. The review provided an up-to-date summary of the predictors of PrEP adherence which provided an empirical basis and informed the development of the empirical article (described below).

The review provided a summary of the key factors related to PrEP adherence amongst actual PrEP users as opposed to previous reviews which had investigated adherence within different study populations (i.e., HIV positive individuals), at earlier points of the prevention cascade (e.g., predictors of uptake) or those which explored hypothetical facilitators and barriers to PrEP use. This meant that review findings were more relevant to the empirical piece and could inform questionnaire development/ the factors which were explored. All key factors highlighted by the review in relation to PrEP adherence were incorporated within the questionnaire used in the empirical piece (e.g. substance use, routine and actual sexual behaviour).

Review findings gave a strong rationale for the methodological design used for the empirical article. The review highlighted factors related to PrEP adherence that may vary situationally (i.e. lifestyle factors; changes in routine, busier schedule, frequent

travel or being away from home) and could influence PrEP adherence in particular contexts. Studies within the review reported that MSM PrEP users showed inconsistent adherence. However, all studies included used correlates of PrEP adherence (e.g. ethnicity) to make comparisons *between* 'good-adherers' and 'poor-adherers' which prevented the investigation of the factors related to variability in adherence across situations *within* an individual. This gave a clear rationale that by using a within-participant design the empirical article could expand upon the review and examine situational variations in adherence.

The review highlighted that studies had not used theory to inform the variables measured in relation to PrEP adherence. Consequently, research has not concluded whether a specific theoretical model accurately explains PrEP adherence. Therefore, it felt necessary that the empirical piece was closely linked to a theoretical model of adherence. Specifically, the review highlighted the potential utility of the IMB model to understand PrEP adherence (Fisher & Fisher, 2002). The review highlighted that this model may be well suited for the empirical piece as it was better placed to acknowledge the complex factors involved in PrEP adherence than other models (e.g. the Necessities-Concerns Framework) (Horne, 2006). Overall, this helped to guide and inform the key psychological constructs investigated in relation to PrEP adherence within the empirical article.

Reflections upon recruitment

The review highlighted the need for future PrEP research to be conducted in diverse settings to increase the generalisability of findings. Originally, the study had intended to recruit from three London sexual health clinics. However, at one site recruitment failed due to impracticalities. For example, rooms were not available to use or clinic slots were not filled with PrEP users at the times I was available. I responded by focusing and recruiting from two sites which were most accessible. At one of these sites, recruitment was limited, mainly again due to impracticalities. In this case, I attended evening clinics but regularly no eligible participants had appointments at these times or I attended the DISCOVER research trial clinic but appointments when I could attend were infrequent (e.g., three participants over the course of a month). This recruitment site had no specific PrEP clinics and alongside my own time-limited restrictions this avenue was impractical. This meant that most participants were sourced from one recruitment site. Recruitment was more successful here as specific PrEP clinics were run monthly and the initiation of the PHE Impact trial meant that large cohorts of new or existing PrEP users were attending the clinic within allotted times to begin their participation in the trial. Recruitment from this one specific site limited the generalisability of results but meant that I could recruit the number of participants needed to adequately power study findings based on a priori power calculations and detect effects of interest.

The review also highlighted the need for research to be conducted in diverse implementation settings and the limitations of examining predictors of PrEP adherence within RCTs. In particular, RCT designs could have overestimated PrEP adherence due to increased resources able to support adherence (e.g., increased monitoring) and different relationships between potential determinants and adherence than would

be found in real-world settings. Therefore, when implemented outside of the context of RCTs, adherence levels and relationships may differ. Originally, the study intended to recruit participants whom were taking part in the PHE Impact pilot project trial delivered through existing sexual-health clinics. This was an opportunity to explore PrEP adherence within 'real-life' clinic settings. However, the time-scales of the Impact implementation were not as expected with clinics projecting that the trial would start much later than expected. Due to time-constraints this would have meant that using this recruitment source for the study would not have been a realistic goal. Therefore, we decided that we would use alternative sources of recruitment (i.e. recruiting existing PrEP users whom obtained PrEP online, via private prescription or were part of the DISCOVER RCT research trial). However, individuals whom actively seek PrEP in this way may be highly motivated to take PrEP and may not be representative of the general MSM PrEP taking population. This meant that the study recruited a cohort of individuals accessing PrEP through specific methods in specific central London clinics which may have limited the generalisability of results.

Reflections upon service user involvement

Arnstein's (1969) ladder of participation, describes different levels of service-user involvement ranging from 'no control' (i.e. service-users as passive consumers) to 'full control' (i.e. where service-users control decision making at the highest level). Using this framework, I think that the current study sits between the 'consultation' (i.e. service-users are asked but have limited influence) and 'participation' (i.e. service-users can make suggestions and influence outcomes) levels. Service-users were not involved in the development of the systematic review and therefore for this component

the research sits within the ‘no control’ section of the hierarchical ladder of participation. However, within the empirical article service user feedback was used to assist questionnaire development. Service-users were sought by advertising on one of the recruitment sites’ social media page. Eight individuals contacted the author and were sent a copy of the draft questionnaire to give feedback in terms of the clarity, relevance, comprehensiveness and any other comments. This led to adaptations to increase relevance for example, changing the names of street drugs, and formatting. Service-users were sent the final questionnaire, meaning they were informed of the influence they had. In this example, service users’ views were sought, taken seriously and had a direct impact on decision making (i.e. meeting criteria for ‘participation’ level service-user involvement). A limitation of this was that the sample size was small and therefore the breadth of feedback and impact of service-user involvement was limited. Due to time constraints, the questionnaire development stage and therefore opportunity for more service-user involvement, was limited. Another limitation was that participants were sent a draft questionnaire and asked to comment upon its content. I think that service-user opinion could have been incorporated more meaningfully/ been more influential if they had been consulted prior to the development of a draft version of the questionnaire (i.e. that service-user involvement would have driven questionnaire development). Further service-user involvement has been planned for the dissemination phase of the project (please see below).

The empirical article met the Department of Health’s (2005) research strategy by involving service users in the design and reporting of research. However, service-users were not involved in the conduct or analysis stages of research. The main reason for not involving service-users during the undertaking of these research processes was due to time and resource constraints (i.e. involving members of the

public to collect or analyse data may have required training which was not viable in the time-frame). However, it would have been useful to consult with service-users at the analysis stage to provide their own interpretations of the data to supplement my own (NIHR, 2010; 2012).

Impact

The World Health Organization (WHO) cites HIV as a major global public health issue, having claimed more than 35 million lives and approximately 1.8 million people becoming newly infected and over a million dying in 2016. While the scale-up of ART treatment has contributed to saving millions of lives and reducing major illnesses, WHO recognises that there has not been the expected impact on HIV incidence at a population level. Newer preventative approaches such as PrEP have been cited as a crucial strategy to provide effective prevention for those at ongoing substantial risk of infection. PrEP implementation has the potential to dramatically reduce HIV acquisition and need for life-long ART adherence (Patel, 2017). However, a barrier to successful PrEP implementation and cost-effectiveness has been non-adherence amongst key high-risk populations (Gomez et al, 2013). The current review and empirical research has investigated the relationship between predictors of adherence to PrEP amongst MSM who are most at risk of HIV acquisition in the UK. This research contributes knowledge regarding the factors which may influence PrEP adherence and indicates ways in which adherence interventions could be tailored to ensure successful PrEP implementation.

Potential Beneficiaries

The potential beneficiaries of this work are a) PrEP users and their sexual partners, b) support organisations, c) clinicians administering PrEP, monitoring PrEP use or delivering PrEP adherence interventions d) policy makers/professionals involved in PrEP implementation guidelines and e) researchers (e.g. health or clinical psychologists) in the PrEP field or examining situationally-specific medication adherence on other conditions.

Non-academic Beneficiaries

PrEP users and their sexual partners

PrEP users engage with PrEP medication as a HIV prevention strategy. The current findings highlight correlates of and situations where non-adherence may be more likely. By summarising and disseminating the key findings across both review and empirical findings for PrEP users, this population may be able to improve their PrEP adherence. For example, PrEP users might be able to pre-plan for high-risk situations for non-adherence (e.g. when they have used substances) if they are prompted to consider which situations are most characteristic of non-adherence for them. If this contributes to increased adherence amongst MSM PrEP users, this may directly benefit the service-user whom may no longer be at risk of HIV acquisition. Helping to ensure that PrEP is an effective HIV prevention tool may also benefit the sexual partners of MSM PrEP users. For example, an HIV-negative MSM PrEP user and their HIV-positive partner may both feel less anxious about HIV transmission during sexual activity if the individual was able to take their PrEP as prescribed.

Support Organisations

Support organisations (e.g. the Terrance Higgins Trust [THT] or the "I want PrEP now" campaign) offer information, support and guidance to individuals to raise awareness of and access to PrEP with the overarching aim to prevent HIV transmission. The current findings could be used and incorporated into their campaigns to help support MSM PrEP users adhere to their medication and potentially prevent HIV acquisition. For example, both THT and I want PrEP now websites give ample information regarding what PrEP is, eligibility, safety profile and potential regimens to follow. However, neither provide adherence support for current PrEP users. Key findings (e.g. normalising and describing potentially high-risk situations for non-adherence such as being away from home) could be reported on these websites. Overall, this would help these organisations support MSM PrEP users during different phases of the prevention cascade.

Clinicians administering PrEP, monitoring PrEP use or delivering PrEP adherence interventions

The empirical article was the first study to explore within-participant predictors of MSM PrEP adherence and the review findings were not substantiated by meta-analysis meaning clinical implications are expressed cautiously. Both pieces highlighted wide-ranging facilitators and barriers to PrEP adherence and the empirical piece highlighted that factors may vary dependent on an individual's situation. In combination, the findings suggest the utility of tailored PrEP adherence interventions which could focus upon situational variations (e.g. variations in mood, information, behavioural skills and behavioural factors). The barriers highlighted could then be used to conceptualise

high-risk situations for non-adherence and alternative strategies could be co-constructed to facilitate adherence in these situations (i.e. a relapse prevention framework). Furthermore, normalising fluctuations of adherence may help PrEP users engage with conversations about their non-adherence and patterns around this. WHO guidelines (2017) recommend 'brief adherence counselling' (not described further) is offered at every follow-up visit. Helping to give clinicians a focus when having these conversations could help to ensure effectiveness and is crucial given current resource and time-limited service settings. Currently there are no standardised assessment tools for PrEP adherence or guidance of how to differentiate PrEP adherence care for individuals.

Policy makers/professionals involved in PrEP implementation guidelines

Policy makers and professionals involved in PrEP guidelines summarise key points for a range of stakeholders to support them in the consideration, planning, introduction and implementation of PrEP. A central aim is to ensure to PrEP effectiveness when implemented in real-life settings. PrEP adherence is a critical determinant of PrEP effectiveness. Therefore, current study findings could be outlined and summarised to provide helpful suggestions how guidelines can be written to facilitate MSM PrEP adherence and ensure PrEP effectiveness.

Academic Beneficiaries

Researchers

Findings highlighted factors that may be related to PrEP adherence and suggested that situational psychological factors are important. This could inform researchers future investigation of the predictors related to PrEP adherence (i.e. inform the variables under investigation or methodological design used) or those examining the theoretical framework which could explain PrEP adherence. Current findings also contribute to a wider literature using a within-participant methodological design to examine adherence within long-term healthcare conditions. Other studies examining adherence within chronic healthcare conditions (i.e. Beta-Thalassaemia-Major and HIV) requiring life-long adherence have also found similar findings (Hawkins et al, 2016; Vosper et al, in. press). This suggests that across conditions there are specific situations that make it difficult to adhere. Therefore, the reach of the current findings may not be limited to researchers investigating adherence in the PrEP using population but also researchers using a within-participant approach to examine adherence within long-term healthcare conditions.

Significance and originality of the work in relation to clinical and health psychology

Clinical and health psychology has a long-history of examining the predictors of adherence to a variety of medical regimens to bridge the gap between biological efficacy of a product/intervention and its effectiveness when implemented in practice (Christensen, 2004). Prior to the current study, no research has specifically examined within-participant predictors of PrEP adherence and more generally this methodological design has been rarely used. The empirical article supports the interpretation that PrEP adherence may vary situationally. This highlights the utility of this methodological design to be able to understand the predictors of adherence. The IMB model has been applied to various physical and mental-health conditions to help explain adherence. At present, there is no established theoretical framework to accurately explain PrEP adherence. Prior to the current study, no study has used theory to inform the choice of variables chosen to measure in relation to PrEP adherence. The empirical piece highlighted the potential utility and robustness of aspects of the IMB model to understand PrEP adherence.

Maximising Impact

To maximise the impact of findings for clinicians, factors highlighted by the review and empirical article could be used to help prompt questions and/or inform the development of standardised questionnaire assessment tools which could ask individuals about key situational factors related to adherence. Clinicians could then efficiently review these forms to orientate and focus conversations on adherence. Alongside these discussions, the development of a standardised assessment tool could highlight individuals who might be most at risk for non-adherence and ensure additional support/service resources were allocated to those most at need (e.g. referrals to adherence interventions or increased monitoring). The empirical study highlighted specific situations where PrEP users were more likely to be non-adherent. These situations could be incorporated within existing problem-solving based PrEP adherence interventions (e.g. NSC) which could help PrEP users identify and cope with these situations (e.g. where they feel less positive affect, lower perceived behavioural skills or are away from home/out of their usual routine).

Time and resource limitations may act as barriers to these discussions. If this were the case, findings could be used to develop informational leaflets regarding factors that may impact adherence, helpful strategies that may maximise adherence and normalising inconsistent use for all PrEP users. This could also be achieved/ facilitated by website and video mediums. Although not a substitute for detailed clinical discussion, these leaflets, if given as part of standard PrEP clinic appointments, would ensure that key points were disseminated to service-users.

Dissemination

Dissemination is one pathway to impact. It is planned that the current research will be made more broadly available by publishing results in a journal article. It is hoped that both the review and empirical article will be published in AIDS & Behavior, a high impact peer-reviewed journal, which focuses upon the psychological and socio-medical aspects of AIDS/HIV and has published multiple articles related to PrEP and PrEP adherence. Due to this journals' scope it is read by wide range of professionals (i.e. clinical and research) from different disciplines helping to facilitate dissemination further. Alongside this, the empirical abstract has also been submitted to the 2018 HIV Research for Prevention conference. This is the only international scientific meeting dedicated to biomedical HIV prevention research and give the opportunity for findings to be disseminated to multiple professionals specifically within this clinical/research domain.

Service-user involvement will be crucial to establish which findings may be most of interest to the public and MSM population. It is planned that I will attend LGBT/MSM specific service-user groups at recruitment sites to not only advise on the most relevant findings but also advise on how results can be presented in format that offers clarity and can be understood by members of the public. It is also hoped that service-users will also provide ideas about where and how findings should be disseminated and potentially be directly involved in presenting the findings. Once this has taken place, findings will be adapted into plain English for dissemination at relevant service user forums. This includes LGBT and MSM specific service user forums at both recruitment sites as well as attending community events. For example, London sexual health clinics run PrEP information evenings and there are independent MSM service-user groups such as IMPULSE which meet to offer support and promote better sexual

wellbeing. It is planned that I will contact and deliver the key findings of the review and empirical project in these settings to facilitate dissemination to service-users. This will not only include PrEP users but those who may not have heard of PrEP, be interested in PrEP uptake or those who have discontinued PrEP, to help ensure that findings are disseminated across stages of the prevention cascade. To not limit the dissemination to service-users who actively attend service-user or community groups it is planned that key findings will be also be disseminated through online mediums. This includes summarising key findings to disseminate on recruitment sites social media platforms such as Facebook, YouTube and Twitter.

To facilitate dissemination to clinicians it is planned that I will attend team meetings and training workshops for staff at London sexual health clinics to present key findings. This could be achieved by contacting existing links with recruitment sites but also with the PrEP Impact trial whom have existing links with multiple London sexual health clinics. To help clinicians translate this information to their practice, leaflets will be made which outlines key findings. This could include a checklist for health care staff (e.g. did you ask whether the person uses reminders? Or has a daily routine?) which may make it easier to translate key findings into a standard part of the assessment format. The impact of this will be maximised if the clinicians see benefit to implementing or changing their practice. Pro-active engagement prior, during and after giving feedback would be crucial to ensure that impact is maximised. This could include conversations with clinicians prior to delivering feedback about what they think would be helpful to their practice. To maximise the impact of this further, I could liaise and develop relationships with existing members of staff. This would mean that current members of staff would be able to become ‘champions’ of the research helping findings to disseminated further.

Lastly, it is hoped that by developing and establishing relationships with multiple potential beneficiaries this will help to maximise the impact of the current study. For example, it is planned that I will communicate via email with drug companies providing PrEP, to key individuals writing PrEP guidelines and to journalists. Following the advice of the Economic and Social Research Journal regarding how to maximise impact and develop relationships with the media, I would contact a small number of specialist journalists who have previously written about PrEP within national papers and gay publications such as the Gay Times Magazine. I could also liaise with the communications team at Royal Holloway University of London to discuss how to draft a press release and where I should send relevant information about the project. Alongside this, it would be helpful to prepare a poster to present to these stakeholders as well as for any unanticipated opportunities that may arise. In sum, it is hoped that these various formats of communication will help to ensure findings are disseminated to multiple stakeholders to enhance reach.

Evidencing Impact

Overall, the impact of the study detailed above suggests that effective dissemination would lead to increased awareness and changes in clinical practice. To demonstrate that these activities had been achieved the impact would have to be evaluated.

To evidence the usefulness of training workshops, my attendance at staff meetings and leaflets given it would be important that clinicians were given the opportunity to give anonymous feedback. This would include asking how much clinicians felt this information had influenced their practice at a later date. This could be given in the form of a simple online questionnaire format which could be circulated via email. It could also provide opportunity for clinicians to feedback what they would find more useful and I could consider these as potential dissemination options. It would also be useful if qualitative research could take place examining the staff experiences of translating key findings into practice at a later timepoint. A similar approach could be taken when evidencing the impact of attending service-user forums.

To gain feedback from social media platforms e.g. Facebook or Twitter a link could be provided to an online questionnaire. This would ask service-users regarding the clarity, relevance and usefulness of the content. It would also ask service-users how this might influence them both generally (e.g. whether they would consider PrEP uptake) and, if relevant, their adherence behaviours. To evidence whether establishing and developing relationships with multiple stakeholders (individuals writing PrEP guidelines, journalists etc) was successful, relevant quotes and excerpts from policy documents that cite the research could be collated.

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Appendices

Appendix 1: Research Ethics Committee provisional approval

1

London - Surrey Borders Research Ethics Committee
Research Ethics Committee (REC) London Centre
Ground Floor
Skipton House
80 London Road
London
SE1 6LH

Telephone: 0207 972 2568
Fax:

27 April 2017

Miss Alison Taylor
Trainee Clinical Psychologist
Camden and Islington NHS Foundation Trust
Department of Psychology
Clinical Psychology Doctoral Programme
Royal Holloway University of London
TW20 0EX

Dear Miss Taylor

Study Title:	**'Psychological and behavioural within-participant predictors of adherence to oral HIV Pre Exposure Prophylaxis (PrEP)'**
REC reference:	**17/LO/0625**
IRAS project ID:	**224366**

The Research Ethics Committee reviewed the above application at the meeting held on 19 April 2017. Thank you and Dr Michael Evangeli for attending to discuss the application.

Provisional opinion

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair in consultation with other Committee members..

Further information or clarification required

1. Submit the full set of final documents to the Committee.
2. Add reference to the use of harder and street drugs to the question on page 3 of the RHUL ART Situational Adherence Questionnaire there is a question 'Were you using alcohol or taking street drugs (e.g. cannabis, ecstasy)...'
3. Please check with NHSE that any involvement in this study would not preclude entry into the NHSE study.

4. Please amend the participant information sheet (PIS) as follows:
    a. Revise point 2) under the section 'Who can take part in the study?' which starts 'had one day ...' as this is difficult to understand. Add 'at least' so this point would read 'at least had one day when you did and at least one day where you did not take your oral PrEP medication in the last month.
    b. Add breaching confidentiality statements to the PIS and consent forms as this is stated in the IRAS form under the confidentiality section, A6-2, page 10 but not included on the PIS or consent form. The committee recommend but this can be adapted or not used at all : *'Everything you say/report is confidential unless you tell us something that indicates you or someone else is at risk of harm. We would discuss this with you before telling anyone else.'*

5. Please amend the consent form as follows:
    a. Change 'tick' to 'initial' after 'please' in the statement 'Have you (please...)'
    b. Add '(please initial)' after 'Do you agree to take part in the study?'
    c. Add a signature strip
    d. Add a title to indicate who the consent form is for.

Recommendation only – not part of the ethical decision

The Committee realise that you may not be able to make these changes as the questionnaire are validated but would like to recommend the following: some of their recommended changes may not be able to implemented these are listed below in the decision section as recommendations only.

1. Make the following changes to the RHUL ART Situational Adherence Questionnaire
    a. Change HIV+ to HIV-
    b. Change the heading '1 Very slightly' to 'Very slightly or Not at all' on the question starting 'How do you feel...' on page 5
    c. Make the same change as above to that on page 9 of the question beginning 'How do you feel ...?'

2. Make the following changes to the LifeWindows Information,,, Questionnaire.
    a. Remove the note from the top as this is not relevant to participants.
    b. Change HIV+ to HIV-
    c. In the question M1 on page 2 change 'realise' to 'think'. The question would then read 'I am worried that other people might think I am ....'.

3. On worksheet 3.1 include an instruction to participants to ignore the scoring instructions.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact REC Manager, Barbara Cuddon, nrescommittee.london-surreyborders@nhs.net

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 27 May 2017.

Summary of the discussion at the meeting

- **Social or scientific value; scientific design and conduct of the study**

The Committee discussed with youthe availability of PrEP in England and Scotland and how this would affect this piece of research. PrEP is available in Scotland but not yet in England. PrEP is only currently available in England if participants take part in a clinical trial.

You confirmed that NHS England is funding a large clinical trial of PrEP before funding it nationally. People in England can access PrEP by private prescription. The aim of the study is to look at adherence to PrEP which is still a relevant question even when PrEP is available in England. Current estimates are that 37% of those taking PrEP do not adhere. This study will look at real life situations of non-adherence. The clinics the research team are working with are already prescribing PrEP on a private basis and some of the clinics will have patients enrolled on the clinical trial. At the present time it is not known whether PrEP will be rolled out in England next year and this study should provide useful data on patterns of adherence. The research team are looking at individuals patterns of adherence. Participants are their own control as this is a 'within participant' study, when participants do and don't adhere.

- **Recruitment arrangements and access to health information, and fair participant selection**

The Committee noted that the protocol states that participants will be offered £5 or £50 in vouchers for taking part but this is not on the IRAS Form.

You explained that it been your original intention to offer participants these payments but Royal Holloway University have agreed that they will not fund participation in this study. The IRAS Form is therefore correct and the protocol is not.

- **Informed consent process and the adequacy and completeness of participant information**

The Committee requested further information of about the consent process - is there an online option?

You confirmed that participants will be given the option of either online or paper consent. For the online consent participants will be given a study ID in the clinic which they will be asked to input before they can complete the survey. They will have been through a verification process to ensure they have capacity to consent. The only piece of identifiable data they will be asked to provide is their date of birth. This will enable them to be withdrawn from the study if they request this and be emailed the outcome of the study.

The Committee alerted you that there were changes they would like made to the PIS and consent form.

- **Suitability of supporting information**

The Committee had noted that at the top of page 3 of the RHUL ART Situational Adherence Questionnaire there is a question 'Were you using alcohol or taking street drugs (e.g. cannabis, ecstasy)...' and asked if reference to the use of harder street drugs could be included.

You agreed this was a good point and agreed to make relevant additions.

There was a discussion with you about the suitability of the questionnaires as a number of issues had been identified on them, for example HIV+ is referred when this population is HIV-, but the Committee were unsure how much these could be changed as they were validated questionnaires.

You and Dr Evangeli explained that during this pilot phase the measurers will be adapted for use with this population. They have previously submitted applications without the final measures before and are keen to have ethical approval for the piloting phase of the project. They do understand that final approval can't be granted until after the piloting stage and the final versions of the measures are submitted. Although the Committee realise that some of their recommended changes may not be able to implemented these are listed below in the decision section as recommendations only.

The Committee responded that to be able to give an ethical decision they have to have the final documents submitted to them and if these measures are going to be substantially changed only a provisional opinion can be given at this stage.

The Committee commented that this is a valuable piece of research for NHS England as this study is about adherence which would be useful as a sub-set to their research.
You and Dr Evangeli confirmed they have discussed their study with NHS England and would welcome any advice from the Committee of the best way to take this forward with NHS England.

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Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [PrEP Adherence Poster Version 1.1 22.03.17]	1.1	22 March 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [2016 - 2017 RSA Professional Indemnity Insurance Schedule]	1.1	22 March 2017
IRAS Application Form [IRAS_Form_24032017]		24 March 2017
IRAS Application Form XML file [IRAS_Form_24032017]		24 March 2017
IRAS Checklist XML [Checklist_24032017]		24 March 2017
IRAS Checklist XML [Checklist_04042017]		04 April 2017
Non-validated questionnaire [Hawkins RHUL ART Situational Adherence Questionnaire]	1.1	22 March 2017
Participant consent form [Consent Form - Version 1.1 22.03.17]	1.1	22 March 2017
Participant information sheet (PIS) [Participant Information Sheet - Version 1.1. 22.03.17]	1.1	22 March 2017
Referee's report or other scientific critique report [Alison Taylor - RHUL Research Sub Committee Feedback and Responses January 2017]	1.1	15 December 2016
Referee's report or other scientific critique report [Alison Taylor - RHUL Research Sub Committee Approval February 2017]	1.1	14 February 2017
Research protocol or project proposal [RHUL Major Research Proposal December 2016]	1.1	03 December 2016
Summary CV for Chief Investigator (CI) [Alison Taylor Curriculum Vitae- IRAS- March 2017]	1.1	22 March 2017
Summary CV for student [Alison Taylor Curriculum Vitae- IRAS- March 201]	1.1	22 March 2017
Summary CV for supervisor (student research) [Evangeli Curriculum Vitae - IRAS - March 2017]	1.1	22 March 2017
Summary CV for supervisor (student research) [Gafos Curriculum Vitae- IRAS - March 2017]	1.1	22 March 2017
Summary CV for supervisor (student research) [Evangeli Curriculum Vitae - IRAS - March 2017]	1.1	22 March 2017
Validated questionnaire [PANAS; Positive and Negative Affect Schedule]	1.1	23 March 2017
Validated questionnaire [The LifeWindows Information-Motivation-Behavioural Skills ART Adherence Questionnaire]	1.1	23 March 2017

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet

6

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

17/LO/0625	**Please quote this number on all correspondence**

Yours sincerely

Sir Adrian Bailllie
Chair

Email: nrescommittee.london-surreyborders@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: *Ms Annette Lock*
Ms Lynis Lewis, Noclor

Appendix 2: Research Ethics Committee favourable opinion

NHS
Health Research Authority

London - Surrey Borders Research Ethics Committee
Research Ethics Committee (REC) London Centre
Ground Floor
Skipton House
80 London Road
London
SE1 6LH

Telephone: 0207 972 2568

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

02 June 2017

Miss Allson Taylor
Trainee Clinical Psychologist
Camden and Islington NHS Foundation Trust
Department of Psychology
Clinical Psychology Doctoral Programme
Royal Holloway University of London
TW20 0EX

Dear Miss Taylor

Study title:	**'Psychological and behavioural within-participant predictors of adherence to oral HIV Pre Exposure Prophylaxis (PrEP)'**
REC reference:	**17/LO/0625**
IRAS project ID:	**224366**

Thank you for your letter of 26 May 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair in consultation with Mr Derek Cook and Dr David Lukey.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will

be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [PrEP Adherence Poster Version 1.1 22.03.17]	1.1	22 March 2017
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only) [2016 - 2017 RSA Professional Indemnity Insurance Schedule]	1.1	22 March 2017
IRAS Application Form [IRAS_Form_24032017]		24 March 2017
IRAS Application Form XML file [IRAS_Form_24032017]		24 March 2017
IRAS Checklist XML [Checklist_24032017]		24 March 2017
IRAS Checklist XML [Checklist_04042017]		04 April 2017
Non-validated questionnaire [ART Situational Adherence Questionnaire- Version 1.2 17.05.17]	1.2	17 May 2017
Non-validated questionnaire [ART Situational Adherence Questionnaire- Version 1.2 17.05.17 Clean Version]	1.2	17 May 2017
Other [REC further information required Version 1.1 10.05.17]	1.1	10 May 2017
Participant consent form [Consent Form - Version 1.2 10.05.17]	1.2	10 May 2017
Participant consent form [Consent Form - Version 1.2. 10.05.17 Clean Version]	1.2	10 May 2017
Participant information sheet (PIS) [Participant Information Sheet - Version 1.2 10.05.17]	1.2	10 May 2017
Participant information sheet (PIS) [Participant Information Sheet - Version 1.2 10.05.17 Clean Version]	1.2	10 May 2017
Referee's report or other scientific critique report [Alison Taylor - RHUL Research Sub Committee Feedback and Responses January 2017]	1.1	15 December 2016
Referee's report or other scientific critique report [Alison Taylor - RHUL Research Sub Committee Approval February 2017]	1.1	14 February 2017
Research protocol or project proposal [RHUL Major Research Proposal December 2016]	1.1	03 December 2016
Summary CV for Chief Investigator (CI) [Alison Taylor Curriculum Vitae- IRAS- March 2017]	1.1	22 March 2017
Summary CV for student [Alison Taylor Curriculum Vitae- IRAS-	1.1	22 March 2017

March 201]		
Summary CV for supervisor (student research) [Gafos Curriculum Vitae- IRAS - March 2017]	1.1	22 March 2017
Summary CV for supervisor (student research) [Evangeli Curriculum Vitae - IRAS - March 2017]	1.1	22 March 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/LO/0625	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

5

Yours sincerely

Sir Adrian Bailllie
Chair

Email:nrescommittee.london-surreyborders@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Annette Lock*
Ms Lynis Lewis, Noclor

Appendix 3: Health Research Authority approval

NHS
Health Research Authority

Miss Allson Taylor
Trainee Clinical Psychologist
Camden and Islington NHS Foundation Trust
Department of Psychology
Clinical Psychology Doctoral Programme
Royal Holloway University of London
TW20 0EX

Email: hra.approval@nhs.net

07 June 2017

Dear Miss Taylor

Letter of HRA Approval

Study title:	**'Psychological and behavioural within-participant predictors of adherence to oral HIV Pre Exposure Prophylaxis (PrEP)'**
IRAS project ID:	**224366**
REC reference:	**17/LO/0625**
Sponsor	**Royal Holloway University of London**

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *'After Ethical Review – guidance for sponsors and investigators'*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

IRAS project ID	224366

procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **224366**. Please quote this on all correspondence.

Yours sincerely

Michael Pate
Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Annette Lock – Royal Holloway University of London – Sponsor contact*
Ms Lynis Lewis – Nocior – Lead NHS R&D contact.

IRAS project ID	224388

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Copies of advertisement materials for research participants [PrEP Adherence Poster Version 1.1 22.03.17]	1.1	22 March 2017
Covering letter on headed paper [Response to HRA Initial assessment]		18 April 2017
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only) [2016 - 2017 RSA Professional Indemnity Insurance Schedule]	1.1	22 March 2017
IRAS Application Form [IRAS_Form_24032017]		24 March 2017
Non-validated questionnaire [ART Situational Adherence Questionnaire- Version 1.2 17.05.17]	1.2	17 May 2017
Non-validated questionnaire [ART Situational Adherence Questionnaire- Version 1.2 17.05.17 Clean Version]	1.2	17 May 2017
Other [Statement of Activities]	1	05 April 2017
Other [Schedule of Events]	1	05 April 2017
Other [REC further information required Version 1.1 10.05.17]	1.1	10 May 2017
Participant consent form [Consent Form - Version 1.2 10.05.17]	1.2	10 May 2017
Participant consent form [Consent Form - Version 1.2. 10.05.17 Clean Version]	1.2	10 May 2017
Participant information sheet (PIS) [Participant Information Sheet - Version 1.2 10.05.17]	1.2	10 May 2017
Participant information sheet (PIS) [Participant Information Sheet - Version 1.2 10.05.17 Clean Version]	1.2	10 May 2017
Referee's report or other scientific critique report [Alison Taylor - RHUL Research Sub Committee Feedback and Responses January 2017]	1.1	22 March 2017
Referee's report or other scientific critique report [Alison Taylor - RHUL Research Sub Committee Approval February 2017]	1.1	22 March 2017
Research protocol or project proposal [RHUL Major Research Proposal December 2016]	1.1	03 December 2016
Summary CV for Chief Investigator (CI) [Alison Taylor Curriculum Vitae- IRAS- March 2017]	1.1	22 March 2017
Summary CV for supervisor (student research) [Evangeli Curriculum Vitae - IRAS - March 2017]	1.1	22 March 2017
Summary CV for supervisor (student research) [Gafos Curriculum Vitae- IRAS - March 2017]	1.1	22 March 2017
Validated questionnaire [PANAS; Positive and Negative Affect Schedule]	1.1	23 March 2017
Validated questionnaire [The LifeWindows Information-Motivation-Behavioural Skills ART Adherence Questionnaire]	1.1	23 March 2017

Appendix 4: Letters of Access/R&D approval

[redacted] [redacted] NHS
NHS Trust

Joint Research Compliance Office
Academic Health Science Centre
Imperial College London and
Imperial College Healthcare NHS Trust
Room 221, Medical School Building
St Mary's Hospital
Praed Street
London W2 1NY
Tel: +44 (0)20 750 41882
r.nicholson@imperial.ac.uk
www.ic.ac.uk/clinicalresearchgovernanceoffice

Ruth Nicholson
Research Governance Manager

17/08/2017

Miss Alison Taylor
Trainee Clinical Psychologist
Camden and Islington NHS Foundation Trust

Dear *Miss Alison Taylor*

Letter of access for research

As an existing NHS employee you do not require an additional honorary research contract with this NHS organisation. We are satisfied that the research activities that you will undertake in this NHS organisation are commensurate with the activities you undertake for your employer. Your employer is fully responsible for ensuring such checks as are necessary have been carried out. Your employer has confirmed in writing to this NHS organisation that the necessary pre-engagement check are in place in accordance with the role you plan to carry out in this organisation. This letter confirms your right of access to conduct research through [redacted] **Trust** for the purpose and on the terms and conditions set out below. This right of access commences on **14/08/2017** and ends on **31/05/2018** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

You are considered to be a legal visitor [redacted] **Trust** premises. You are not entitled to any form of payment or access to other benefits provided by this organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through [redacted] **Trust**, you will remain accountable to your employer **Camden and Islington Trust** but you are required to follow the reasonable instructions of your nominated manager **Dr** [redacted] in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with [redacted] **Trust** policies and procedures, which are available to you upon request, and the Research Governance Framework.

[redacted] [redacted] NHS
NHS Trust

You are required to co-operate with [redacted] Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on [redacted] Trust premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and the Trust [redacted] **Trust** prior to commencing your research role at the Trust.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

[redacted] Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.
Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or suitability to work with adults or children, or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the NHS organisation that employs you through its normal procedures. You must also inform your nominated manager in this NHS organisation.

[redacted]

[redacted] NHS

NHS Trust

Yours sincerely

Ms Ruth Nicholson
Research Governance Manager

cc: Researcher designated manager in the Trust
HR department of the substantive employer

[redacted] NHS Foundation Trust

Department of Research and Development
Research Delivery Team Office
Unit G2, Ground Floor, Harbour Yard
Chelsea Harbour
London SW10 0XD

28th July 2017

Miss Alison Taylor
Department of Psychology
Clinical Psychology Doctoral Programme
Royal Holloway University of London
TW20 0EX

Dear Alison,

Letter of Access for Research

This letter should be presented to your nominated manager at each participating site within this organisation before you commence your research at [redacted] NHS Foundation Trust.

In accepting this letter [redacted] NHS Foundation Trust confirms your right of access to conduct research through this organisation for the purpose and on the terms and conditions set out below. This right of access commences on **28th July 2017** and ends on **31st May 2018** unless terminated earlier in accordance with the clauses below. **If you require an extension to your letter of access, you must inform the Research and Development office, at least one month in advance.**

This letter of access is for research activities in relation to the following **only**:

Study title:	**Psychological and behavioural within-participant predictors of adherence to oral HIV Pre Exposure Prophylaxis (PrEP)**
IRAS reference:	**224366**
REC reference:	**17/LO/0625**
Local reference:	**C&W17/057**

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from [redacted] NHS Foundation Trust. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from the department of research and development giving confirmation of their agreement to conduct the research.

The information supplied about your role in research at this organisation has been reviewed and you do not require an honorary research contract with this organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. Evidence of checks should be available on request to this organisation.

You are considered to be a legal visitor to the organisation premises. You are not entitled to any form of payment or access to other benefits provided by [redacted] NHS Foundation Trust to employees and this letter does not give rise to any other relationship between you and this organisation, in particular that of an employee.

While undertaking research through this organisation you will remain accountable to your substantive employer but you are required to follow the reasonable instructions of this organisation or those instructions given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with this organisation's policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with this organisation in discharging its duties under the Health and Safety at Work Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and [redacted] NHS Foundation Trust prior to commencing your research role.

You are required to ensure that all information regarding patients or staff remains secure and **strictly confidential** at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on this organisations premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this organisation does not accept responsibility for damage to or loss of personal property.

This organisation may revoke this letter and terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of

any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this organisation or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you must stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager, [redacted] in this organisation and the department of research and development in this organisation.

Yours sincerely,

Damon Foster
Research Delivery Operations Manager
[redacted]NHS Foundation Trust

Appendix 5: Substantial Amendment approval

NHS
Health Research Authority

London - Surrey Borders Research Ethics Committee
Research Ethics Committee (REC) London Centre
Ground Floor
Skipton House
80 London Road
London
SE1 6LH

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

13 September 2017

Ms Annette Lock
Doctorate in Clinical Psychology, Royal Holloway University of London
Egham
TW20 0EX

Dear Ms Lock

Study title:	**'Psychological and behavioural within-participant predictors of adherence to oral HIV Pre Exposure Prophylaxis (PrEP)'**
REC reference:	**17/LO/0625**
Amendment number:	**SA01**
Amendment date:	**29 August 2017**
IRAS project ID:	**224366**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Non-binding advice:
The Sub-Committee encourages the researcher to ensure that all members of the clinic team practise excellent GCP to ensure the rights, safety and well-being of patients and the quality of the research data.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	SA01	29 August 2017
Research protocol or project proposal	1.2 Clean	17 August 2017
Research protocol or project proposal	1.2 Tracked	17 August 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/LO/0625:	**Please quote this number on all correspondence**

Yours sincerely

PP Ms. Christine Braithwaite
Chair

E-mail: nrescommittee.london-surreyborders@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Lynis Lewis, Nocior*
Miss Allson Taylor, Camden and Islington NHS Foundation Trust

London - Surrey Borders Research Ethics Committee

Attendance at Sub-Committee of the REC meeting in Correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Ms. Christine Braithwaite	Director of Standards and Policy	Yes	
Mr Thomas Morrish	Clinical Research Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Patrycja Pysz	REC Assistant

Appendix 6: Royal Holloway University of London College Ethics Committee approval

Memorandum

To: Alison Taylor

From: Gary Brown (on behalf of the Research Sub-Committee and Course Executive)

Date: 14th February 2017

Copy To: Michael Evangeli

Re: Main Research Project Proposal

The Research Sub-Committee has considered your Main Research Project Proposal response and Systematic Review Checklist and has decided to give you **Approval.** Your research costs have also been approved. Please note that if these costs change and you do not re-submit an amended form for approval prior to incurring any additional costs, these additional costs will not be reimbursed**.**

Now that you have received approval it is time to apply for ethics. Please keep Annette informed and where possible provide copies of all applications, letters and approvals. **Also, please ensure that if RHUL is your sponsor, Annette is sent all participant signed consent forms.**

Appendix 7: Life Windows Questionnaire

The LifeWindows Information-- Motivation -- Behavioral Skills ART Adherence Questionnaire (LW-IMB-AAQ) ITEMS

Note: Each LW-IMB-AAQ item represents a barrier primarily falling within the I (Information), M (Motivation), or B (Behavioral Skills) constructs. When used with the LifeWindows ART adherence intervention software program, a 'critical zone' is superimposed for a range of response options for each item (reflected here as shaded and in red text). Responses within the critical zone are interpreted as signaling the presence of a deficit or potential deficit that then triggers the offering of intervention activities specifically developed to address the barrier reflected in the content of the item.

I1 I know how each of my current HIV medications is supposed to be taken (for example whether or not my current medications can be taken with food, herbal supplements, or other prescription medications).

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I2 I know what to do if I miss a dose of any of my HIV medications (for example, whether or not to take the pill(s) later).

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I3 Skipping a few of my HIV medications from time to time would not really hurt my health.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I4 I know what the possible side effects of each of my HIV medications are.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I5 As long as I am feeling healthy, missing my HIV medications from time to time is OK.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I6 I understand how each of my HIV medications works in my body to fight HIV.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I7 If I don't take my HIV medications as prescribed, these kinds of medications may not work for me in the future.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

I8 I believe that if I take my HIV medications as prescribed, I will live longer.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

I9 I know how my HIV medications interact with alcohol and street drugs.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M1 I am worried that other people might realize that I am HIV+ if they see me taking my HIV medications.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M2 I get frustrated taking my HIV medications because I have to plan my life around them.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M3 I don't like taking my HIV medications because they remind me that I am HIV+.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M4 I feel that my healthcare provider takes my needs into account when making recommendations about which HIV medications to take.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M5 Most people who are important to me who know I'm HIV positive support me in taking my HIV medications.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly Agree ☐ No one that I care about knows I am positive

M6 My healthcare provider doesn't give me enough support when it comes to taking my

medications as prescribed.

I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

M7 It frustrates me to think that I will have to take these HIV medications every day for the rest of my life.

I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

M8 I am worried that the HIV medications I have been prescribed will hurt my health.

I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

M9 It upsets me that the HIV medications I have been prescribed can affect the way I look.

I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

M10 It upsets me that the HIV medications I have been prescribed can cause side effects.

I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

B1 There are times when it is hard for me to take my HIV medications when I drink alcohol or use street drugs.

I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree	I don't drink alcohol or use street drugs

B2 How hard or easy is it for you to stay informed about HIV treatment?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy

B3 How hard or easy is it for you to get the support you need from others for taking your HIV medications (for example, from friends, family, doctor, or pharmacist)?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy

B4 How hard or easy is it for you to get your HIV medication refills on time?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B5 How hard or easy is it for you to take your HIV medications when you are wrapped up in what you are doing?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B6 How hard or easy is it for you to manage the side effects of your HIV medications?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B7 How hard or easy is it for you to remember to take your HIV medications?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B8 How hard or easy is it for you to take your HIV medications because the pills are hard to swallow, taste bad, or make you sick to your stomach?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B9 How hard or easy is it for you to make your HIV medications part of your daily life?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B10 How hard or easy is it for you to take your HIV medications when your usual routine changes (for example, when you travel or when you go out with your friends)?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B11 How hard or easy is it for you to take your HIV medications when you do not feel good emotionally (for example, when you are depressed, sad, angry, or stressed out)?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B12 How hard or easy is it for you to take your HIV medications when you feel good physically and don't have any symptoms of your HIV disease?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B13 How hard or easy is it for you to take your HIV medications when you do NOT feel good physically?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B14 How hard or easy is it for you to talk to your health care provider about your HIV medications?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

Appendix 8: Participant Information Sheet

Psychological and behavioural within-participant predictors of adherence to oral HIV Pre- Exposure Prophylaxis (PrEP)

Participant Information Sheet

You have been asked to participate in a study about adherence to oral PrEP, which is being carried out by Alison Taylor, trainee clinical psychologist, in collaboration with Site 1, Site 2 and Site 3 clinics.

Thank you for your interest in the research study. Please read the following information carefully:

What is the study about?

The aim is to explore adherence to oral PrEP. PrEP works to reduce HIV transmission but a high level of adherence is necessary for it to be effective. The study focuses on whether there are particular situations, beliefs and feelings which are linked with whether individuals take or do not take their daily oral PrEP medication. We believe our findings will help the development of tailored interventions to improve PrEP adherence.

Who can take part in the study?

You have been approached to participate because you have been prescribed oral PrEP medication. To participate in this study, you must have:

1) been prescribed oral PrEP medication for at least three months **and**
2) follow a daily dosing regimen **and**
3) had at least had one day where you did and at least one day where you did not take your oral PrEP medication in the last month.

What will the study involve?

There is just one part to this study: you will be asked to fill out questionnaires about one time that you did and one time that you didn't take oral PrEP medication in the previous month. You will also be asked some background questions about yourself. These questionnaires could be completed either online or on paper. Alternatively, you could choose to complete the questionnaire on the phone or in an interview with the researcher. These questionnaires should take no longer than 30 minutes to complete.

Do I have to take part?

Taking part in the research is completely voluntary and you may withdraw from the study at any time, without giving a reason. If you decide to take part (or not) this will not affect the standard of your care in anyway.

What are the risks of taking part?

We do not think there are any particular risks associated with taking part in the research. However, if you feel worried or distressed during the study please feel free to contact the researcher (details provided below). A list of support services will be presented at the end of the survey, however, you will also be able to access support from the clinic (i.e. Site 1, Site 2 or Site 3) if required.

What are the benefits of taking part?

One potential benefit of taking part in this research is that you may find it helpful to reflect on periods when you have and haven't taken your oral PrEP medication. You may also find it a positive experience to know that you are informing research which would go on to help other people taking PrEP. For example, results could help inform the way clinicians support adherence in others using oral PrEP medication.

Is it confidential?

Yes. Your information and responses will be kept completely confidential unless you tell us something that indicates you or someone else is at risk of harm. We would discuss this with you before telling anyone else. You will be assigned a unique number to identify you throughout the study. All data will be stored in a password-protected database that only the research team will have access to. The research team includes; Alison Taylor, (Trainee Clinical Psychologist, Royal Holloway University of London (RHUL)), **Dr Michael Evangeli (Senior Lecturer at RHUL)** and **Dr Mitzy Gafos (Associate Professor, The London School of Hygiene & Tropical Medicine)**.

We will ask you to provide an email address to be sent a summary of the study findings. This is optional. If you choose to provide this information, your email addresses will be stored in a separate password-protected database from your responses; there will be no direct association between your email addresses and your responses.

What will happen to the results of the study?

The research will be submitted in partial fulfilment of a doctorate degree in Clinical Psychology. We aim to publish its results in a peer-reviewed journal and at conferences. The published data will be anonymised and no participants will be identified. If you would like, we will send you a summary of the findings via the email address you provide.

Who is organising and funding the research?

The research is being led by Alison Taylor and is being funded by Royal Holloway, University of London (RHUL), as part of the doctorate programme in Clinical Psychology. This study has been reviewed and approved in accordance with xxx NHS ethics committee as well as the College Ethics Committee at RHUL.

Who should you contact with questions?

This project is supervised by **Dr Michael Evangeli (Clinical Psychologist and Senior Lecturer at Royal Holloway University London)** and **Dr Mitzy Gafos (Associate Professor, The London School of Hygiene & Tropical Medicine)**.
The main person to contact for this project is Alison Taylor, Trainee Clinical Psychologist as the Department of Clinical Psychology, Royal Holloway University of London (RHUL). You can get in touch in the following ways if you have any questions about the research at any time.

- Email: alison.taylor.2015@live.rhul.ac.uk
- Phone: 01784 414012 (this is an answering message- please say your message is for Alison Taylor, leave a message clearly stating your name and phone number.)

Who should you contact with a complaint?

If you have any complaints about this research or how it is conducted please contact the Patient Advice and Liaison Service (PALS) who can offer confidential advice, support and information:

- Site 1 participants, please contact the w and x PALS on: xxxx xxx xxxx.
- Site 2 participants, please contact the y PALS on: xxxx xxx xxxx.
- Site 3 participants, please contact the z PALS on: xxxx xxx xxxx.

Thank you very much for taking the time to read the information sheet. If you are happy to participate, please complete the consent form on the next page.

Appendix 9: Consent Form

Consent form- For Participant

Project Title: Psychological and behavioural within-participant predictors of adherence to oral HIV Pre-Exposure Prophylaxis (PrEP)

Name of researcher: Alison Taylor (alison.taylor.2015@live.rhul.ac.uk)
You have been asked to participate in a study about adherence to oral PrEP, which is being carried out by Alison Taylor, trainee clinical psychologist at Royal Holloway University of London, in collaboration with Site 1 and Site 2.

Have you (please initial):

	Yes	No	Not Applicable
Read and understood the information sheet about the above study?			
Had the opportunity to ask questions?			
Got satisfactory answers to your questions?			
Understood that participation is voluntary and you are free to withdraw from the study at any time? (without giving reason and without it affecting your care)			
Understood that your information will be kept confidential throughout the research process, unless you tell us something that indicates you or someone else is at risk of harm. (We would discuss this with you before telling anyone else.)			

Do you agree to take part in the study? (please initial)
Yes
No

Participant Signature:_____

Participant please print name here: _____

Researcher Signature:_____

Appendix 10: Final Questionnaire

ART Situational Adherence Questionnaire

Demographic Information:

Your date of birth **(DD/MM/YYYY) format**:

……..

Occupational status **(please tick):**

Employed Full Time	☐	Employed Part Time	☐	Unemployed	☐	Student Full Time	☐	Student Part Time	☐
Retired	☐	Other	☐						

Highest educational qualification **(please tick):**

Not Applicable	☐	GCSE /O-level	☐	A-level/ BTEC	☐	Degree level Qualification	☐	Postgraduate Qualification	☐

Ethnicity **(please tick):**

White	☐	Black	☐	Asian	☐	Mixed	☐	Other	☐

If other, **please specify:**

……

Born in the UK? **(please tick):**

Yes	☐	No	☐

Relationship status **(please tick):**

Single	☐
Partner, living together	☐
Partner, living separately	☐

Number of sexual partners in the last month **(please write):**

……..

How long have you been taking PrEP for? **(please tick):**

3-4 months ☐ 5-8 months ☐ 9-12 months ☐ 1 year+ ☐

How do you obtain your PrEP medication? (please tick):

Online ☐ Private Prescription ☐ Research/Study Participant ☐ Friend ☐ Other ☐

If 'other' please specify where you obtain PrEP:

……

Do you have a daily routine for when/how you take your PrEP? (please tick)

Yes ☐ No ☐

What clinic do you attend for PrEP monitoring? (please tick):

Site 1 ☐ Site 2 ☐ Site 3 ☐

Following your daily dosing regimen, how many times have you taken your medication in the last 7 days? (please write):

…….

Are you experiencing side effects? (please tick):

Yes ☐ No ☐

If Yes, are these side effects distressing you? (please tick):

Yes ☐ No ☐ N/a ☐

Please take a moment to think about a time when you did take your PrEP. For example, think about where you were, how you were feeling, what you expected to do that day or who you expected to see.

Think about the time when you **did take** your PrEP.
Please answer these questions about what you thought and how you felt at that time.

What day of the week was it **(when you <u>did</u> take your PrEP)?:**

…….

Please write how many days ago this was **(when you <u>did</u> take your PrEP)** e.g. 2 days ago, 3 days ago etc?:

……

Was there someone there or did you have other prompts e.g. pill box or alarm to remind you to take your PrEP at the time? **(please circle):**

Yes No

Please tick which one applied to you at the time **(when you <u>did</u> take your PrEP) (please tick):**

My day was the same as normal ☐
My day was different to normal because of something unexpected ☐
My day was different to normal because I had made plans ☐
Other ☐

Where were you? **(when you <u>did</u> take your PrEP) (please tick):**

Own home ☐ A friend's house ☐ Partner's house ☐
A public place (e.g. work or college) ☐ Somewhere else ☐

If you ticked 'somewhere else' **please specify:**

……

Who were you with? (when it was time to take your PrEP and you <u>did</u> take it) **(please tick):**

Alone ☐ With a friend ☐ With a partner ☐ With family ☐
With an acquaintance ☐ With a work colleague☐ Someone else ☐

If you ticked 'someone else' **please specify:**

……

If you weren't alone, did this person/these people know you were taking PrEP? **(please circle):**

Yes No N/a

Were you using alcohol or taking drugs (e.g. cannabis, ecstasy, G, crystal meth/Tina, mephedrone) around the time you took your PrEP? **(please circle):**

Yes No

How likely did you think it was that you were going to have sex on that day? **(please circle):**

Very Unlikely	Unlikely	Neither likely or unlikely	Likely	Very Likely
1	2	3	4	5

Did you have sex on that day? **(please circle):**

Yes No

When you were due to take your medication, to what extent did you feel you were at risk of HIV without taking PrEP? **(please circle):**

Very Unlikely	Unlikely	Neither likely or unlikely	Likely	Very Likely
1	2	3	4	5

If you did have sex on that day, did the person you had sex with know you were taking PrEP? **(please circle):**

Yes No N/a

If you did have sex on that day, did you use a condom? **(please circle):**

Yes No N/a

If you did have sex on that day, was this chemsex? **(please circle):**

Yes No N/a

If you did have sex on that day, what was the status of your sexual partner **(please circle):**

HIV negative HIV positive Don't know N/a

If you did have sex on that day, was this **(please circle one or more):**

Anal insertive (top) Anal receptive (bottom) Oral sex

Other N/a

If you did have sex on that day, was this with a casual or regular partner? **(please circle):**

Casual partner Regular partner N/a

*Please again, take a moment to think about a time when **you did** take your PrEP. For example, think about where you were, how you were feeling, what you expected to do that day or who you expected to see.*

At the time I was due to take my PrEP…

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
I knew the correct way to take my medicines	☐	☐	☐	☐	☐
I knew how taking PrEP could make me feel	☐	☐	☐	☐	☐
I understood how my PrEP would work	☐	☐	☐	☐	☐
I knew I should take the PrEP at that time	☐	☐	☐	☐	☐
I thought other people would notice I was taking my PrEP and think I was HIV positive which concerned me	☐	☐	☐	☐	☐
I thought that other people would notice me taking PrEP and think I was promiscuous, which bothered me	☐	☐	☐	☐	☐
I knew how to tell others about my PrEP use	☐	☐	☐	☐	☐
I thought I had to plan my life around my medicine, which frustrated me	☐	☐	☐	☐	☐
PrEP reminded me I was at risk of HIV, which bothered me	☐	☐	☐	☐	☐
I felt confident that my PrEP was going to work	☐	☐	☐	☐	☐

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
People around me that I care about were supportive about my PrEP	☐	☐	☐	☐	☐
I thought that I would have to take these medicines every day during the time I was at risk, which I did not like	☐	☐	☐	☐	☐
I thought my PrEP might interact with other substances/drugs I was taking, which bothered me	☐	☐	☐	☐	☐
I thought that taking PrEP might stop me from taking precautions against STI's, which bothered me	☐	☐	☐	☐	☐
I thought that taking PrEP was easier than using a condom	☐	☐	☐	☐	☐
I thought PrEP would make me worry less about HIV	☐	☐	☐	☐	☐
I thought PrEP would make me enjoy sex more	☐	☐	☐	☐	☐
I thought PrEP was harming me	☐	☐	☐	☐	☐
I thought PrEP would cause side effects	☐	☐	☐	☐	☐
I had easy access to my medicines	☐	☐	☐	☐	☐

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
I was confident I could find the time to take my PrEP	☐	☐	☐	☐	☐
I was confident I could manage any side effects	☐	☐	☐	☐	☐
I was confident that I could remember to take my medicines	☐	☐	☐	☐	☐
I was confident I could manage the size of the pills or the taste of the medicine	☐	☐	☐	☐	☐
I felt confident that I had enough PrEP for other days	☐	☐	☐	☐	☐
I felt confident that I could fit my medicines around what I was doing	☐	☐	☐	☐	☐
I felt confident I could take my medicines correctly	☐	☐	☐	☐	☐
I felt confident I could take my medicines even if other people were around	☐	☐	☐	☐	☐
I felt confident I could ask for help to take my PrEP if I needed to	☐	☐	☐	☐	☐
I felt confident I could take my medicines however I was feeling	☐	☐	☐	☐	☐
I felt ill	☐	☐	☐	☐	☐

How did you feel when it was time to take your PrEP?

	1 Very slightly or Not at all	2 A little	3 Moderately	4 Quite a bit	5 Extremely
Active	☐	☐	☐	☐	☐
Afraid	☐	☐	☐	☐	☐
Determined	☐	☐	☐	☐	☐
Nervous	☐	☐	☐	☐	☐
Attentive	☐	☐	☐	☐	☐
Upset	☐	☐	☐	☐	☐
Inspired	☐	☐	☐	☐	☐
Hostile	☐	☐	☐	☐	☐
Alert	☐	☐	☐	☐	☐
Ashamed	☐	☐	☐	☐	☐

ART Situational Adherence Questionnaire

*Now please take a moment to think about a time when **you did not** take your PrEP. For example, think about where you were, how you were feeling, what you expected to do that day or who you expected to see.*

Think about the time when you **did not take** your PrEP.
Please answer these questions about what you thought and how you felt at that time.

What day of the week was it **(when you did not take your PrEP)?:**

……

Please write how many days ago this was **(when you did not take your PrEP)** e.g. 2 days ago, 3 days ago etc?:

……

Did you forget to take your PrEP or did you intentionally not take your medication? **(please tick):**

I forgot ☐ I chose to not take my medication ☐

If you chose not to take your PrEP please write why:

……..

Was there someone there or did you have other prompts e.g. pill box or alarm to remind you to take your PrEP at the time? **(please circle):**

Yes No

Please tick which one applied to you at the time **(when you <u>did not</u> take your PrEP):**

My day was the same as normal ☐
My day was different to normal because of something unexpected ☐
My day was different to normal because I had made plans ☐
Other ☐

Where were you? **(when you <u>did not</u> take your PrEP) (please tick):**

Own home ☐ A friend's house ☐ Partner's house ☐
A public place (e.g. work or college) ☐ Somewhere else ☐

If you ticked 'somewhere else' **please specify:**

.....

Who were you with? **(**when it was time to take your PrEP and you <u>did not</u> take it) **(please tick):**

Alone ☐ With a friend ☐ With a partner ☐ With family ☐
With an acquaintance ☐ With a work colleague☐ Someone else ☐

If you ticked 'someone else' **please specify:**

.....

If you weren't alone, did this person/these people know that you were taking PrEP? **(please circle):**

Yes No N/a

Were you using alcohol or taking drugs (e.g. cannabis, ecstasy, G, crystal meth/Tina, mephedrone) around the time you were meant to take your PrEP? **(please circle):**

Yes No

How likely did you think it was that you were going to have sex on that day? **(please circle):**

Very Unlikely	Unlikely	Neither likely or unlikely	Likely	Very Likely
1	2	3	4	5

Did you have sex on that day? **(please circle):**

Yes No

When you were due to take your medication, to what extent did you feel you were at risk of HIV? **(please circle):**

Very Unlikely	Unlikely	Neither likely or unlikely	Likely	Very Likely
1	2	3	4	5

If you did have sex on that day, did this person you had sex with know you were taking PrEP? **(please circle):**

Yes No N/a

If you did have sex on that day, did you use a condom? **(please circle):**

Yes No N/a

If you did have sex on that day, did you use **post**-exposure prophylaxis (i.e. PEP medication)? **(please circle):**

Yes No N/a

If you did have sex on that day, was this chemsex? **(please circle):**

Yes No N/a

If you did have sex on that day, what was the status of your sexual partner **(please circle):**

HIV negative HIV positive Don't know N/a

If you did have sex on that day, was this **(please circle one or more):**

Anal insertive (top) Anal receptive (bottom) Oral sex

Other N/a

If you did have sex on that day, was this with a casual or regular partner? **(please circle):**

Casual partner Regular partner N/a

*Please again, take a moment to think about a time when **you did not** take your PrEP medication. For example, think about where you were, how you were feeling, what you expected to do that day or who you expected to see.*

At the time I was due to take my PrEP…

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
I knew the correct way to take my medicines	☐	☐	☐	☐	☐
I knew how taking PrEP could make me feel	☐	☐	☐	☐	☐
I understood how my PrEP would work	☐	☐	☐	☐	☐
I knew I should take the PrEP at that time	☐	☐	☐	☐	☐
I thought other people would notice I was taking my PrEP and think I was HIV positive which concerned me	☐	☐	☐	☐	☐
I thought that other people would notice I was taking my PrEP and think I was promiscuous which bothered me	☐	☐	☐	☐	☐
I knew how to tell others about my PrEP use	☐	☐	☐	☐	☐
I thought I had to plan my life around my medicine, which frustrated me	☐	☐	☐	☐	☐
PrEP reminded me I was at risk of HIV, which bothered me	☐	☐	☐	☐	☐
I felt confident that my PrEP was going to work	☐	☐	☐	☐	☐

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
People around me that I care about were supportive about my PrEP	☐	☐	☐	☐	☐
I thought that I would have to take these medicines every day during the time I was at risk, which I did not like	☐	☐	☐	☐	☐
I thought my PrEP might interact with other substances/drugs I was taking, which bothered me	☐	☐	☐	☐	☐
I thought that taking PrEP might stop me from taking precautions against STI's, which bothered me	☐	☐	☐	☐	☐
I thought that taking PrEP was easier than using a condom	☐	☐	☐	☐	☐
I thought PrEP would make me worry less about HIV	☐	☐	☐	☐	☐
I thought PrEP would make me enjoy sex more	☐	☐	☐	☐	☐
I thought PrEP was harming me	☐	☐	☐	☐	☐
I thought PrEP would cause side effects	☐	☐	☐	☐	☐
I had easy access to my medicines	☐	☐	☐	☐	☐

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
I was confident I could find the time to take my PrEP	☐	☐	☐	☐	☐
I was confident I could manage any side effects	☐	☐	☐	☐	☐
I was confident that I could remember to take my medicines	☐	☐	☐	☐	☐
I was confident I could manage the size of the pills or the taste of the medicine	☐	☐	☐	☐	☐
I felt confident that I had enough PrEP for other days	☐	☐	☐	☐	☐
I felt confident that I could fit my medicines around what I was doing	☐	☐	☐	☐	☐
I felt confident I could take my medicines correctly	☐	☐	☐	☐	☐
I felt confident I could take my medicines even if other people were around	☐	☐	☐	☐	☐
I felt confident I could ask for help to take my PrEP if I needed to	☐	☐	☐	☐	☐
I felt confident I could take my medicines however I was feeling	☐	☐	☐	☐	☐
I felt ill	☐	☐	☐	☐	☐

How did you feel when it was time to take your PrEP?

	1 Very slightly or Not at all	2 A little	3 Moderately	4 Quite a bit	5 Extremely
Active	☐	☐	☐	☐	☐
Afraid	☐	☐	☐	☐	☐
Determined	☐	☐	☐	☐	☐
Nervous	☐	☐	☐	☐	☐
Attentive	☐	☐	☐	☐	☐
Upset	☐	☐	☐	☐	☐
Inspired	☐	☐	☐	☐	☐
Hostile	☐	☐	☐	☐	☐
Alert	☐	☐	☐	☐	☐
Ashamed	☐	☐	☐	☐	☐